Does electron density in *bond critical point* reflect the formal charge distribution in H-bridges? The case of charge-assisted hydrogen bonds (CAHBs)

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ABSTRACT

The charge-assisted hydrogen bond (CAHB) was investigated for a set of H-bridges of N–H···Cl type. The properties of these bonds, i.e. interaction energy and electron density measured in a specific point of the bond, were represented as functions of H···Cl distance. It appears that the energy of interaction is very strongly affected by formal charges, which may be explained by the presence of efficient interaction between formal ions. Surprisingly, the electron density measured in the H-bond critical point is totally independent of the formal charges. For the given H···Cl distance the ρ_{BCP} value is the same, no matter whether neutral molecules or oppositely charged ions interact with each other.

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1. Introduction

Among different so-called "weak interactions" the hydrogen bond (H-bond) has probably been most thoroughly investigated. This is due to the fact that this interaction plays an essential role in many physical, chemical and biological processes [1–8]. The strongest and, therefore, having the greatest impact on the properties of interacting molecular groups are H-bonds assisted with additional effects. A good example of such an interaction is the resonance-assisted hydrogen bond (RAHB) [9] and the charge-assisted hydrogen bond (CAHB) [10]. The concept of RAHB was originally proposed by Gilli et al. [9] and later developed by those authors [11–16]. (It is fair to mention here that a criticism of RAHB was also formulated [17–20].) According to the original concept of RAHB stronger H-bonding in this case results from the contribution of charge-separated resonance structure which favors the formation of H-bond, as shown in Fig. 1. Thus, it may be said that in fact the distribution of formal charge in a given resonance structure is indirectly responsible for relatively stronger H-bonding in RAHB motifs.

The direct interaction between charge distribution and H-bonding strength occurs in CAHB in the case of which formal positive charge on the proton-donating atom, CAHB(+), or formal negative charge on the proton-accepting group, CAHB(−), additionally stabilizes the H-bonding [12,21–27]. See Fig. 2 for

examples. The case of the so-called salt bridge, also designed as CAHB(+/−) or *double charge-assisted hydrogen bonds* is particularly interesting. In this case both proton-donating and proton-accepting centers carry the formal opposite charges (Fig. 2c). This type of CAHB, obviously dominated by the ionic character of interaction, can be found for instance in crystal structures of ammonium chloride and its other halogen analogs. For a recent review devoted to H-bond theory, including CAHB see Ref. [28].

It has been proven in many articles that the properties of electron density function may reflect the strength and the character of bonding in question. Topological analysis of electron density function based on Atoms in Molecules Quantum Theory (QTAIM) proposed by Bader [29,30] was successfully used to characterize different chemical bonds, e.g. covalent bonds [29,31,32], metal–ligand interactions [33–36], different kinds of H-bonds [4,37–40], including dihydrogen bonds [41] and the so-called hydrogen–hydrogen interactions [42–47], as well as for other weak noncovalent interactions [48–51]. (It is worth to mention here, that the concept of hydrogen–hydrogen interactions was criticized by some authors. See for instance Refs. [52,53].) In the case of all those interactions the amount of electron density measured at the so-called bond critical point (BCP, the $(3, -1)$ saddle point on electron density curvature being a minimum in the direction of the atomic interaction line and a maximum in the two directions perpendicular to it), is connected with the bonding energy (although some important exceptions were also reported [54,55]). This observation may be explained by the general concept of chemical bonding as a phenomenon resulting from the presence of electrostatic forces

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PAPER

Does the concept of Clar's aromatic sextet work for dicationic forms of polycyclic aromatic hydrocarbons?—testing the model against charged systems in singlet and triplet states†

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The concept of Clar's π-electron aromatic sextet was tested against a set of polycyclic aromatic hydrocarbons in neutral and doubly charged forms. Systems containing different types of rings (in the context of Clar's concept) were chosen, including benzene, naphthalene, anthracene, phenanthrene and triphenylene. In the case of dicationic structures both singlet and triplet states were considered. It was found that for singlet state dicationic structures the concept of aromatic sextet could be applied and the local aromaticity could be discussed in the context of that model, whereas in the case of triplet state dicationic structures Clar's model rather failed. Different aromaticity indices based on various properties of molecular systems were applied for the purpose of the studies. The discussion about the interdependence between the values of different aromaticity indices applied to neutral and charged systems in singlet and triplet states is also included.

Introduction

In 1972 Erich Clar published his book entitled "*The aromatic sextet*"[1] where he introduced an original concept that makes it possible to explain several physical and chemical properties of polycyclic aromatic hydrocarbons (PAHs). According to that concept π-electrons forming delocalized double bonds, *e.g.* in the benzene ring (with the π-electron structure often considered as a superposition of localized Kekulé structures),[2] belong to an aromatic sextet *localized* within that ring. Additionally, according to Clar's concept, if more than one canonical structure can be considered for a given system, then those of them which have the highest number of localized sextets are the most stable structures. Such structures are called *Clar structures*. In the case of a benzene molecule consisting of a single benzenoid ring it rather is not justified to consider the difference between Kekulé-type resonance structures and Clar's localized sextet. However, if we take into consideration the PAHs, the difference between these two concepts appears to be crucial. Let us explain the case of phenanthrene, *i.e.* PAH consisting of three fused benzene rings. Scheme 1 shows two (out of five possible) Kekulé structures of phenanthrene and corresponding to them two structures with localized sextets denoted as the circles within the rings. Obviously, according to
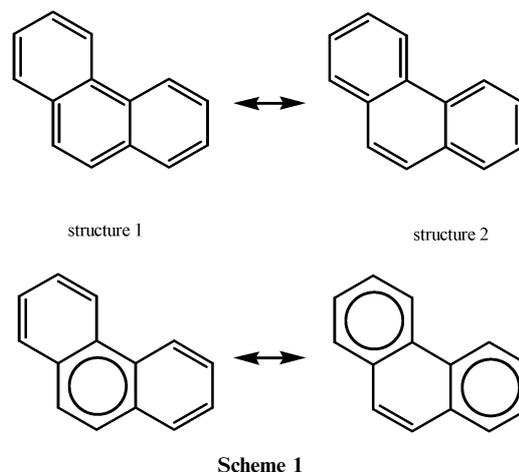
Scheme 1

Clar's concept, structure 2 is more stable, as it contains the greatest possible number of localized sextets. Therefore, this structure can be called the Clar structure. In fact, the lateral rings in phenanthrene are significantly more aromatic than their inner counterpart. This was shown using several indicators of aromaticity.[3–10] Thus, it can be concluded that structure 2 (in meaning of Clar's structure or its Kekulé equivalents) contributes more to the superposition of all resonance structures that are possible for phenanthrene. In the case of the topological analogue of phenanthrene, *i.e.* the anthracene, the situation is significantly different. There are three structures, equivalent from the point of view of Clar's concept, in which there is always only one Clar's sextet localized in one of the three

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Aromaticity of substituted fulvene derivatives: substituent-dependent ring currents†

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Patrick W. Fowler[*e] **and Andrew D. McKenzie**[e]

Fulvene is a non-aromatic molecule, but variation of the electron-donating/withdrawing power of substituents *exo* to the five-membered ring can drive the system between the extremes of aromatic and antiaromatic, as judged by prediction of fully developed diatropic and paratropic ring currents through *ab initio* calculations made at the ipsocentric 6-31G**/CTOCD-DZ CHF level.

Introduction

As a non-alternant hydrocarbon, fulvene differs significantly from its better known isomer, benzene.[1] Benzene is a thermodynamically and kinetically stable system, whereas fulvene is not. Estimates of resonance energy per (π) electron (REPE) for fulvene are systematically lower than those for benzene: the Dewar REPE for fulvene and benzene are $+0.023$ and $+0.220$ eV,[2] respectively; the REPE values estimated by Hess and Schaad[3] are -0.003 eV and $+0.092$ eV; the most recent data for the aromatic stabilization energies (ASE) of the two species are -3.1 and $+32.4$ kcal mol^{-1} (6×-0.022 eV and 6×2.34 eV), respectively.[4] Fulvene is chemically reactive,[5] unlike benzene, which is rather inert[1,6] and, if it does react, shows a tendency to retain its π-electron structure, favouring substitution over addition.[7] Where substituent effects on molecular geometry are detected, *e.g.*, in mono-substituted benzene derivatives, the effect can be ascribed mainly to variations in electronegativity of the substituent, and is most pronounced for the bond angles of the ring.[8,9] The influence of these substituents on the π-electronic structure of the ring structure is small.[10] In contrast, exocyclic substitution in fulvene leads to dramatic changes in π-electronic structure and aromaticity: the more electron donating the substituent, the more aromatic the ring becomes. Changes in aromaticity indices are found to be related linearly to substituent constants (σ^+),[11] and the impressive precision of this relation leads to a new way of evaluating such constants.[12] Various indicators, *e.g.*, aromatic stabilization energies (ASE), nucleus independent shifts (NICS), exaltation of magnetic susceptibility and the geometry-based harmonic oscillator model of aromaticity (HOMA), all seem more or less equally capable of representing the rathe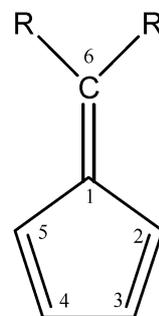r homogenous trends in substituent structural effects.[13] Structural correlations with aromaticity have been made for puckered benzenes using measures of angular strain, a technique which could be applied to isomeric non-planar fulvenes.[14] Combinations of structural, electric and magnetic properties have been used to probe aromaticity of some exotic fulvene systems, in which the CH_2 group is replaced successively by SiH_2, GeH_2, SnH_2, SiF_2, GeF_2, and SnF_2 groups.[15,16]

One unambiguous criterion of aromatic character in cyclic systems, which underlies all other magnetic indices, is the existence of an induced ring current in the presence of an external magnetic field. The previous considerations suggest substantial substituent-induced changes in the current-density map of fulvene, even to the extent of the growing-in of a full ring current with increase in electron-donating power of the substituent. The present paper subjects this prediction to a direct theoretical test, by *ab initio* calculation of current-density maps of fulvene and examples of 6-substituted derivatives. The current-density results are shown to fit within the general trends for the influence of substituents, as predicted by calculation of substituent-induced changes in π electron populations. Population shifts are judged from the π electron density parameter, pEDA,[17] which itself is found to correlate well with empirical Hammett substituent constants.

Methods

Geometries

For the background study of π-electronic population and charge-transfer, a large set of fulvene derivatives was assembled in which one or two substitutions were made at

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† Electronic supplementary information (ESI) available: HOMA and pEDA data for 29 fulvene derivatives. See DOI: 10.1039/c003686b

Scheme 1 Atom labelling in substituted fulvene derivatives.

organic compounds

8-Phenyl-3,4,6,7,8,8a-hexahydro-1H-pyrrolo[2,1-c][1,4]oxazin-6-one

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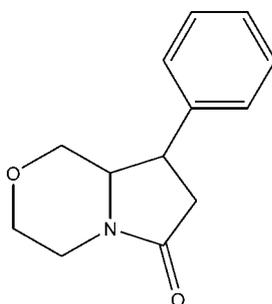Correspondence e-mail: malecka@uni.lodz.pl

In the title compound, $C_{13}H_{15}NO_2$, the hexahydropyrrolo[2,1-c][1,4]oxazine fragment is disordered over two conformations (A and B) in a 0.656 (5):0.344 (5) ratio. The five-membered ring is similarly disordered and adopts an envelope conformation in A, while in B this ring is nearly planar [maximum deviation = 0.088 (1) Å]. The six-membered rings in both A and B exhibit chair conformations. In the crystal, weak intermolecular C—H···O hydrogen bonds link the molecules into ribbons propagating in [010].

Related literature

For the synthesis, see: Leśniak et al. (2009). For bond-length data, see: Allen et al. (1987). For the biological properties of similar structures, see: Nicolaou et al. (2002). For related structures, see: Chaume et al. (2008); Dorsey et al. (2003); Harwood et al. (1997).

Experimental

Crystal data

$C_{13}H_{15}NO_2$	$V = 1091.72$ (15) Å^3
$M_r = 217.27$	$Z = 4$
Monoclinic, $P2_1/c$	Mo $K\alpha$ radiation
$a = 13.2737$ (12) Å	$\mu = 0.09$ mm^{-1}
$b = 7.1066$ (4) Å	$T = 100$ K
$c = 11.9233$ (10) Å	$0.36 \times 0.21 \times 0.03$ mm
$\beta = 103.917$ (7)°	

Data collection

Stoe IPDS 2 diffractometer	1200 reflections with $I > 2\sigma(I)$
6960 measured reflections	$R_{int} = 0.108$
2301 independent reflections	

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.047$	H atoms treated by a mixture of independent and constrained refinement
$wR(F^2) = 0.109$	
$S = 0.81$	$\Delta\rho_{max} = 0.21$ e Å^{-3}
2301 reflections	$\Delta\rho_{min} = -0.27$ e Å^{-3}
196 parameters	

Table 1
Hydrogen-bond geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
C2—H2B···O2[i]	0.97	2.46	3.329 (3)	149
C7A—H7A···O1[ii]	0.97	2.43	3.154 (4)	131

Symmetry codes: (i) $x, y - 1, z$; (ii) $-x + 1, y + \frac{1}{2}, -z + \frac{3}{2}$.

Data collection: *X-AREA* (Stoe & Cie, 2000); cell refinement: *X-AREA*; data reduction: *X-RED* (Stoe & Cie, 2000); program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *PLATON* (Spek, 2009); software used to prepare material for publication: *PLATON*.

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Routes of π-Electron Delocalization in 4-Substituted-1,2-benzoquinones[†]

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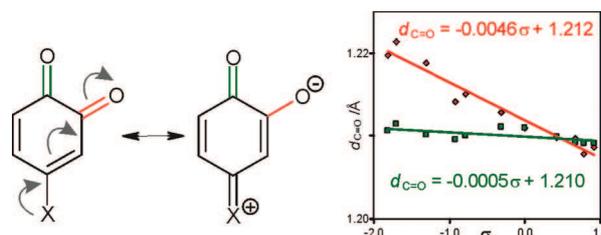
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The substituent effect in 4-substituted-1,2-benzoquinone is investigated by means of modeling using B3LYP hybrid functional in conjunction with the 6-311+G(d,p) basis set. The interrelation between different types of substituents, X = NO, NO_2, CN, CHO, H, Me, OMe, OH, NH_2, NHMe and $N(Me)_2$, and both CO groups has been characterized both qualitatively and then quantitatively by means of several measures of π-electron delocalization (HOMA, MCI, DI, FLU) based on structural and electronic properties of 4-substituted-1,2-benzoquinones chosen for analysis. Results of this analysis clearly show that only the meta-placed CO group is affected by substituents, whereas the para-placed CO group is rather insensitive to substitution. These observations may help to explain diversified chemical properties (including reactivity) of CO centers in *o*-benzoquinone derivatives. Among others, they may explain differences in proton-accepting properties of carbonyl O atoms, as it is shown for simple models in which carbonyl groups in *o*-benzoquinone act as proton acceptors in H-bonds of O···H−F type.

Introduction

It has long been known that substituent effect from meta- and para-positions differs in a dramatic way. Quantitatively

it was shown in a clear manner already by Hammett himself in his fundamental monograph[1] by introducing two kinds of substituent constants σ_m and σ_p. Taft et al.[2] quantified this difference by assuming that for para-substituent effect the

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(1) Hammett, L. P. *Physical Organic Chemistry*; McGraw Hill: New York, London, 1940; p 188.

Electron Density Characteristics in Bond Critical Point (QTAIM) versus Interaction Energy Components (SAPT): The Case of Charge-Assisted Hydrogen Bonding

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S *Supporting Information*

ABSTRACT: Charge-assisted hydrogen bonds (CAHBs) of N—H···Cl, N—H···Br, and P—H···Cl type were investigated using advanced computational approach (MP2/aug-cc-pVTZ level of theory). The properties of electron density function defined in the framework of Quantum Theory of Atoms in Molecules (QTAIM) were estimated as a function of distance in H-bridges. Additionally, the interaction energy decomposition was performed for H-bonded complexes with different H-bond lengths using the Symmetry-Adapted Perturbation Theory (SAPT). In this way both QTAIM parameters and SAPT energy components could be expressed as a function of the same variable, that is, the distance in H-bridge. A detailed analysis of the changes in QTAIM and SAPT parameters due to the changes in H···A distance revealed that, over some ranges of H···A distances, electrostatic, inductive and dispersive components of the SAPT interaction energy show a linear correlation with the value of the electron density at H-BCP ρ_{BCP}. The linear relation between the induction component, E_{ind}, and ρ_{BCP} confirms numerically the intuitive expectation that the ρ_{BCP} reflects directly the effects connected with the sharing of electron density between interacting centers. These conclusions are important in view of charge density studies performed for crystals in which the distance between atoms results not only from effects connected with the interaction between atomic centers directly involved in bonding, but also from packing effects which may strongly influence the length of the H-bond.
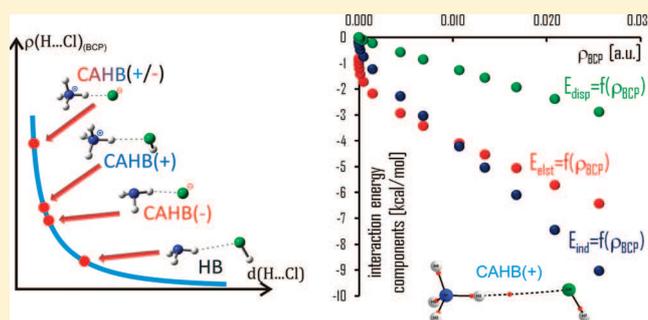
INTRODUCTION

Hydrogen bonding (H-bonding) plays an essential role in many physical, chemical and biological processes.[1−8] Among different types of H-bonds those assisted by additional effects are the strongest. A good example can be the resonance-assisted hydrogen bonding (RAHB) that, according to the original concept proposed by Gilli et al.,[9,10] is relatively stronger than other H-bonds because of the effect of resonance proceeding along the sequence of covalent bonds linking the proton-accepting group with the proton-donating one. In other words the contribution of charge-separated structures additionally stabilizes this type of H-bonding. Another example of the H-bonding strengthened by an additional effect is the so-called charge-assisted hydrogen bonding (CAHB).[11−17] In this case the strengthening of H-bond results from the specific distribution of the charge in ion—ion or ion—neutral molecule complexes. Therefore, the different types of CAHBs can be defined on the basis of formal charge distribution in H-bridge (see Scheme 1).

The CAHBs(+) are classified as interactions in which the cationic proton-donating fragment interacts with the formally neutral proton-accepting group. Consequently, the CAHBs(−) are the H-bridges in which the formally neutral proton-donating

group interacts with the anionic proton-accepting group. The most interesting situation appears when the cationic proton-donating group interacts with the anionic proton-accepting group. The H-bonds of this type are classified as the so-called salt bridges, also known as CAHB(+/−) or *double charge-assisted hydrogen bonds*. Since CAHBs are stronger than noncharge-assisted H-bonds (non-CAHBs), they obviously have a larger impact on physical and chemical properties of the chemical species involved in complexation. For the strongest H-bonds the partially shared character of interaction was observed.[18] This issue is addressed in detail in a recent review on covalency of H-bonding.[19]

Quantum Theory of Atoms in Molecules[20,21] (QTAIM) gives the unique possibility to have an insight into a region of a system on the basis of physical properties of that system, i.e. it gives a possibility to divide the system (e.g., a molecule) into subsystems (e.g., atoms) on the basis of zero-flux in the electron density gradient field. Since the majority of chemists are interested in the

Basis Set and Method Dependence in Atoms in Molecules Calculations

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The influence of various basis sets used in HF and DFT/B3LYP calculations to the values of atoms in molecules (AIM) parameters derived from the electron density distibution for weak hydrogen-bonded systems is investigated. Using three model complexes, $F_3CH\cdots NH_3$, $F_3CH\cdots NCH$, and $FCCH\cdots NH_3$, we show that values of the most important AIM parameters calculated in the bond critical point of the $H\cdots N$ hydrogen bond are almost independent of both the method and the basis set. Only the smallest Dunning-type cc-pVDZ or aug-cc-pVDZ basis sets may lead to poor results, whereas even medium-sized Pople-type basis sets can give reasonable results converting to those obtained from the use of large Dunning-type basis sets.

Introduction

All atomic and molecular properties are governed by the electron density distribution. Thus, the methods that deal with the analysis of the electron density distribution should have a particular appeal for chemists and help to understand the electron structure of molecules and thus interactions. Important information about the charge distribution and about its changes due to intermolecular interactions can be obtained by means of population analysis, where the total number of electrons is divided to individual atoms or even to atomic orbitals. The most popular are the population analysis introduced by Mulliken[1] and Löwdin.[2] Still increasing weight is also attached to the natural bond orbital (NBO) method proposed by Weinhold et al.[3]

All these methods try to represent the molecule as a distribution of point charges. Unfortunately, *their definitions are basis set dependent* and specify some characteristic points that reflect the use of atom-centered basis sets. This disadvantage of traditional methods of the electron density distribution is remedied in the atoms in molecules (AIM) theory of Bader.[4−9] A great interest and widespread use of this method is due to the fact that, as opposed to the wave function quantum mechanics, the AIM method gives the opportunity to have an insight into a region of a system. This opportunity meets the interest of most chemists who wish to have a theoretical tool to study a small part of a molecule only, instead of dealing with the total energy of a whole system.

The goal of the AIM theory is to find a *physically well-defined* surface that divides a system to subsystems. In the AIM theory the surface bounding the subsystem is established by the electron density gradient vector field ($\vec{\nabla}\rho$). More strictly, this bounding surface is established is such a way that there must not be a flux in $\vec{\nabla}\rho$ through the surface. Thus a surface satisfying this condition is known as "a zero flux surface".[7] This surface passes through a point called a critiacal point (CP), where $\vec{\nabla}\rho = \vec{0}$.

Of particular interest is a critical point in which the electron density is a minimum with respect to the direction of a line connecting two nuclei and a maximum with respect to all directions perpendicular to this line, thus being a saddle point with the $(3,-1)$ curvature. A critical point with such characteristics is called a bond critical point (BCP) and indicates the accumulation of the electron density. Thus BCP can be used in the recognition of chemical bonds between atoms and then in studies of the character of this interatomic interaction.

Large attention is paid to the proper values of the electron density, ρ_{BCP}, and its Laplacian, $\nabla^2\rho_{BCP}$, in BCP of the $XH\cdots Y$ interaction, since they may indicate a hydrogen bond if these parameters have proper values.[10] The Laplacian of ρ_{BCP} has a dominant role in the AIM analysis, since it determines where the electron density is locally concentrated ($\nabla^2\rho < 0$) and depleted ($\nabla^2\rho > 0$) within a molecular system.[5] Moreover, $\nabla^2\rho_{BCP}$ is related[6] to the local potential and kinetic energy densities ($V(\vec{r})$ and $G(\vec{r})$, respectively) that are components of H, the total energy density.

Most of AIM calculations are performed with the use of rather small basis sets; thus one may ask about the dependence of values of AIM parameters on both the basis set and the method used in AIM calculations. In other words, one may ask about the reliability of such calculations, i.e., about the stability of values of AIM parameters with respect to the change of both the basis set and the method used in AIM calculations. The aim of this paper is to study this issue.

Methodology

To study the stability of AIM calculations with respect to the basis set and the method, we chose three model complexes: $F_3CH\cdots NH_3$, $F_3CH\cdots NCH$, and $FCCH\cdots NH_3$. The choice of weak hydrogen-bonded systems was thought to find differences between values of AIM parameters (if any) on various levels of approximation, since all variations due to the use of a given basis set and method should be a substantial part of investigated AIM parameters. Various AIM parameters commonly used in the description of inter- and intramolecular interactions were then computed using a large set of medium and large basis sets of Pople[11] and Dunning[12,13] type. Small basis sets of the Pople type were not used in this paper since they give unsatisfactory results in calculations concerning intermolecular interactions. HF[11] and DFT/B3LYP[14−17] approximations were used.

Geometry optimizations were performed at the level of B3LYP/aug-cc-pVTZ for collinear arrangement of individual monomers to use symmetry relations and thus to simplify

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Experimental and theoretical electron-density study of three isoindole derivatives: topological and Hirshfeld surface analysis of weak intermolecular interactions

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A combined experimental and theoretical study of three isoindole derivatives was made on the basis of a topological analysis of their electron-density distributions. Experimental electron densities were determined from high-resolution X-ray diffraction data sets measured with synchrotron radiation at 100 K, whereas theoretical calculations were performed using DFT methods at the B3LYP\6-311++G(3df,3pd) level of approximation. Both experimental and theoretical models are in good agreement with each other. Since the analysed structures possess a variety of hydrogen-bonding interactions, weak intermolecular contacts of $C-H\cdots C(\pi)$, $C,N(\pi)\cdots C,N(\pi)$ and $H\cdots H$ types were subject to our special interest and are discussed in detail. They were characterized quantitatively and qualitatively by topological properties using Bader's Atoms in Molecules theory and by mapping the electron-density distribution, electrostatic potential and a geometric function on the Hirshfeld surface. This way the forces and directions of intermolecular interactions as present on the molecular surfaces were depicted and described. These interactions not only guide crystal packing, but are likewise important for recognition processes involving (aza)isoindole fragments in a biological environment.

1. Introduction

The 3-substituted isoindol-1-ones have attracted our attention since they represent an important structural unit found in biologically active compounds, natural products and synthetic intermediates. Typical examples of pharmaceutically interesting molecules possessing anxiolytic activity are: pazinaclone (Wada & Fukuda, 1991), pagoclone (Sorbera *et al.*, 2001) and zopiclone (Anzini *et al.*, 1996; Gotor *et al.*, 1997). Moreover, the azaisoindol-1-one moiety also features in benzopyran derivatives used in the treatment of hypertension (American Home Products Corporation, 1997) and it may be useful as a synthetic precursor of simplified analogues of the INH-NAD adducts with potential interest as antituberculosis drugs (Broussy *et al.*, 2005).

Herein we report the experimental and theoretical electron-density studies of three isoindole derivatives: 3-hydroxy-2-phenyl-2,3-dihydro-isoindol-1-one (I), 5-hydroxy-6-phenyl-5,6-dihydro-pyrrolo[3,4-*b*]pyridin-7-one (II) and (3*S*)-3-hydroxy-2,3-diphenyl-2,3-dihydro-pyrrolo[3,4-*c*]pyridine-1-one (III) (see Fig. 1). High-resolution X-ray diffraction experiments using synchrotron radiation at low temperature allowed us to extract the precise electron-density distribution of (I)–(III) from the crystalline state, whereas DFT calculations verified the models obtained. The results were interpreted according to the 'Quantum Theory of Atoms in Molecules' (QTAIM) of Bader (1990), which is a powerful

Reaction of 3,3′,4,4′-tetramethyl-1,1′-diphosphaferrocene with [Re₂(CO)₈(CH₃CN)₂]: Novel coordination modes of the 1,1′-diphosphaferrocene ligand

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Abstract

Reaction of 3,3′,4,4′-tetramethyl-1,1′-diphosphaferrocene (**1**) with [Re₂(CO)₈(CH₃CN)₂] afforded two trimetallic complexes in which the heterometallocene is ligated across the Re–Re bond. The structure of the complex having **1** bridging the Re₂(CO)₈ moiety through two P atoms was determined by X-ray diffraction and compared with those of analogous complexes with organic bridging bis-phosphines. The second complex obtained in this reaction presumably contains **1** acting as a (P,Fe) bridging ligand.
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Keywords: 1,1′-Diphoshaferrocene; Rhenium carbonyl; Bridging ligand; X-ray structure

1. Introduction

1,1′-Diphosphaferrocenes, discovered by Mathey et al. [1], display rich coordination chemistry due to the presence of lone pairs of electrons at the phosphorus atoms [2–7]. In fact, the η¹-coordination to one and two metal centres (structures **A** and **B**, respectively), as well as the chelate coordination of both phosphorus atoms to one metal centre (structure **C**) and bridging of two-metal centres through one P atom (structure **D**) are well evidenced. Some of such complexes are efficient catalysts [7].
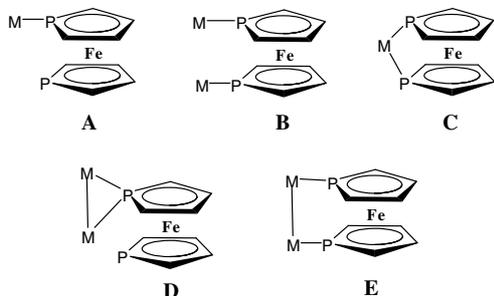
Logically, 1,1′-diphosphaferrocenes should also act as bidentate ligands spanning two directly bonded metal centres in metal clusters (structure **E**). This coordination mode, which is typical for organic bis-phosphines [8], along with unusual electronic properties [2] and redox-activity [9] would make 1,1′-diphosphaferrocenes very interesting ligands for chemistry of polynuclear complexes.

Attempts to obtain complexes of the type **E** in reaction of 3,3′,4,4′-tetramethyl-1,1′-diphosphaferrocene (**1**) with bimetallic compounds Co₂(CO)₈ and Mn₂(CO)₁₀ failed, resulting only in the decomposition or formation of complexes of the type **A** or **B**, where M is a two-metal entity [2]. This failure has been tentatively explained by mismatch between the P–P distance in the *syn*-conformation of **1** and the **M**–**M** distance in the metal carbonyl backbone (the latter distance being markedly shorter). However, in light of theoretical calculations showing that the phosphorus-atom lone pairs in **1** have essentially spherical *s* character [7], which should enable adoption of this ligand to various geometries around metal centre(s) this argument does not seem justified.

In this communication, we report that reaction of **1** with the labile [Re₂(CO)₈(CH₃CN)₂] complex leads to

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Halogen bond, hydrogen bond and N···C interaction – On interrelation among these three noncovalent interactions

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ABSTRACT

The analysis of interrelation among halogen bond, hydrogen bond and weak N···C interaction in the $(CH_3X)(HNC)(HCN)$ complexes (X = Cl, Br) was performed on the basis of MP2 calculations. The model system was chosen for the complexes in such a way that all three interactions stabilize the complexes consisting of three molecular fragments. Both two-body additive contributions and three-body nonadditive contributions to the total interaction energy are discussed. Additionally, interaction energy decomposition was performed with the use of SAPT, such that both two- and three-body contributions were also estimated. QTAIM was used for topological analysis of electron density. In the case of investigated complexes both hydrogen bond and N···C interaction predominate over halogen bond. The SAPT results indicate that the electrostatic contribution to interaction energy dominates for the hydrogen bond and the N···C interaction, while the dispersion component is mostly responsible for the halogen bonding, which is weakest of all. The QTAIM analysis reveals that the noticeable transfer of electron charge occurs only between the molecular fragments forming the hydrogen bond. Finally, we establish the influence of CP-corrected optimization and MP2 variant on the geometries and interaction energies of the complexes.

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1. Introduction

Since last a few years the halogen bond (X-bond) became one of the most thoroughly investigated noncovalent interaction [1,2]. This is due to the fact that this interaction is responsible for several physical and chemical properties exhibited by various molecular species [3–14]. Although the mechanism of formation of X-bond seems to be well recognized, still some discrepancies regarding its origin can be noticed in the literature. In general it has been thoroughly accepted that the anisotropy of charge distribution of halogen atom is the property being responsible for X-bond formation [1,15–24]. In the consequence of that anisotropy the partial positive charge occurs at the extension of the bond between the halogen and the adjacent atom. Since this positive charge can interact with a center possessing local negative charge concentration (lone pairs, π-electrons, etc.), it has been postulated that the X-bond is an electrostatically driven interaction [1]. There are, however, studies which show that purely electrostatic nature of this interaction can be questionable and that partially covalent character resulting from e.g. charge transfer, orbital overlapping, induction, etc. can be at least equally important in the case of X-bonding [15,25–28]. Therefore, X-bond is often considered as Lewis acid–Lewis base interaction in which molecular fragment

with the halogen atom acts as Lewis acid, that is, the electron acceptor. Although the final agreement about the X-bond nature has not been reached yet, undoubtedly the anisotropy of charge distribution is always considered as this basic property of the halogen atom, which lays directly in the foundation of the mechanism of X-bond formation. The term "sigma-hole" is also used in the context of X-bond [29], since the region of partial positive charge (the "hole") is placed at the extension of the sigma bond between halogen atom and the other atom (usually carbon) bonded to it. The classic X-bond is characteristic of these species in which halogen atom is bonded to carbon atom, preferably of sp^3 type [1]. However, this is not any particular restriction and X-bonds with contribution of halogen atom linked to e.g. aromatic carbon were also observed [30]. It is also important to mention that X-bond usually can be observed for heavier halogen atoms, with the strength increasing with the size of the halogen. X-bonds with contribution of fluorine atom acting as Lewis acid are rather uncommon, if they exist at all [28].

The halogen atom possesses lone pairs, and as such it may also act as a Lewis base. Recently one of us had shown that halogen atom may act not only as Lewis acid, but may reflect the dual character, being Lewis acid in the direction opposite to the R–X bond and simultaneously the Lewis base in direction perpendicular to that bond, and that these properties of halogen atom can be explained with the spatial distribution of HOMO and LUMO orbitals [26]. More recently Grabowski [31] explained the nature of
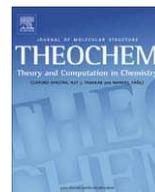
On the nature of halogen bond – The Kohn–Sham molecular orbital approach

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ARTICLE INFO

ABSTRACT

The nature of halogen bonding is investigated for a set of H_3C—X...O=CH_2 and F_3C—X...O=CH_2 (X = Cl, Br, I) molecular complexes. The Kohn–Sham MO investigation indicates effective stabilizing charge transfer/polarization interaction, while electrostatic interaction contributes only slightly to the total bonding interaction, being systematically overbalanced by exchange repulsion. Thus, the covalent nature of halogen bonding may be expected on the basis of the obtained results. What is more, the halogen atom, being Lewis acid in halogen bonding, may simultaneously act as Lewis base in hydrogen bonding. The same mechanism of anisotropic charge distribution on halogen atom is responsible for this dual character.

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1. Introduction

Among the so-called non-covalent interactions the hydrogen bond (H-bond) is probably most frequently and thoroughly investigated. This is due to the fact that H-bond plays an essential role in many physical, chemical and biochemical processes [1–3]. However, recently increasing attention has been paid to other intermolecular interactions. Currently, halogen bonding seems to be one of the most intensively investigated such interaction, since it has been found that this interaction shares many properties with H-bond. In fact, it has been reported that halogen bonding may be competitive to H-bond, and similarly as H-bond, it may play the crucial role in structure stabilization of crystals [4–6] and biomolecular systems [7,8] and also may be used in new drug design and material engineering [9,10]. In the literature halogen bonding is usually explained in terms of the electrostatic potential on the surface of X [7,11,12]. It was found that halogen atoms X in R—X (where R is usually the σ-electron withdrawing moiety) have a surprising feature; a partial positive electrostatic potential centered on the region of space being opposite to the R—X bond. In this way the interaction between halogen atom and some negative charge concentration, e.g. lone electron pair located on oxygen or nitrogen atom, can be observed. Thus, halogen bonding is usually considered as the electrostatic interaction between the positive region on the halogen and a lone pair of a Lewis base [7,11–16].

In this paper it is demonstrated by means of Kohn–Sham MO based interaction energy decomposition that the nature of halogen

bonding is rather close to the nature of charge transfer/polarization interaction, partially covalent in its character, and that electrostatic interaction contributes only slightly to the total stabilizing interaction.

2. Methodology

All calculations were based on DFT [17–20] and performed with the use of ADF package [21]. BP86 functional [22,23] was applied in combination with a large uncontracted set of Slater-type orbitals (STOs) containing diffuse functions, that is, the valence-split quadruple-ζ basis set augmented with four sets of polarization functions (QZ4P in ADF). Scalar relativistic effects for all atoms were accounted for by means of zeroth-order regular approximation (ZORA) [24]. Full electron calculations were performed (no frozen core approximation was applied). Equilibrium geometries were fully optimized using analytical gradient techniques. All structures were verified to be energy minima through a vibrational analysis. The BP86 functional was chosen since it was recently reported that this functional gives very reasonable results for weak interaction, e.g. those of hydrogen bond type [25]. It should be emphasized that the full electron QZ4P basis set combined with ZORA approach gives the results that are very close to the basis limit (BSSE correction is practically meaningless in this case).

Bonding analysis of the X...O (X = Cl, Br, I) was performed according to quantitative bond energy decomposition scheme implemented in ADF [26]. According to this bonding analysis the overall interaction energy ΔE_{tot} consists of two major components:

$$\Delta E_{tot} = \Delta E_{prep} + \Delta E_{int}$$

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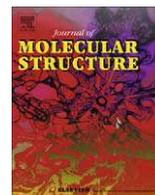
Synthesis, structural and conformational study of chromane derivatives

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ABSTRACT

2-Methyl-4-oxo-4H-chromene-3-carboxylic acid methyl ester (**1**) and 2-phenyl-4-oxo-4H-chromene-3-carboxylic acid ethyl ester (**2**) were reacted with NaBH$_4$ to give 2-R-2,3-dihydro-4-hydroxy-2H-1-benzopyran-3-carboxylic acid esters (**3**: methyl ester, R = methyl, **4**: ethyl ester, R = phenyl – respectively). The structures of resultant compounds **3** and **4** were confirmed by IR, ^{1}H NMR spectroscopy, mass spectrometry and elemental analysis. Additionally the X-ray analysis of the compound **3** revealed that hydrogen atoms bonded to the C2 and C4 atoms are in axial positions and hydrogen atom bonded to C3 atom is in equatorial position. The main conformation in solution for both compounds is similar and was confirmed based on the $^3J_{HH}$ coupling constants obtained from experimental spectra and from DFT conformational analysis.

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1. Introduction

For many years the research in our laboratory has been directed towards the synthesis of chromone (benzo-γ-pyrone) and coumarin (benzo-α-pyrone) derivatives and the study of their reactivity towards nucleophilic reagents containing nitrogen, oxygen, sulfur and carbon [1]. In particular, chromones in protolytic solvents have been efficiently converted at room temperature into enamine-type compounds with a typical lemon-yellow color [2,3]. In addition, both type of compounds (chromones and coumarins) exhibit interesting biological properties [4,5], including anticonvulsant, antimicrobial, spasmolytic, antioxidant and antitumor activities. What is more remarkable chromone moiety is a part of the structure of vitamin E which plays an important role as biological antioxidant [6]. For many years our interest was focused on the synthesis, and elucidation of structure and biological properties of chromones [7], coumarins [1] and flavanones [8]. The chromane and its derivatives flavanones are abundant in natural products that possess a broad range of biological activity. The biological antioxidant vitamin E is a principal scavenger of peroxyl radicals in biological membrane [9].

Elucidation of compounds structure is possible not only by means of X-ray crystallography. NMR experiments are also useful in determining the shape of the molecular moiety. For example dependence between $^3J_{HH}$ coupling constant and the dihedral angle, first analyzed by M. Karplus [10], is useful in determination of three dimensional structure of compound. Unfortunately equation derived by M. Karplus is not universal. It means that coupling constant is strongly dependent on the chemical environment and thus the functional form needs to be adjusted to considered case. Quantum calculations are especially helpful in such considerations, as they can be the source of information about several different compounds with known and different values of particular dihedral angle without the need of synthesizing those compounds.

Herein we report the synthesis of a novel 2-R-2,3-dihydro-4-hydroxy-2H-1-benzopyran-3-carboxylic acid esters (**3**: methyl ester, R = methyl, **4**: ethyl ester, R = phenyl) in the reaction of 2-methyl-4-oxo-4H-chromene-3-carboxylic acid methyl ester (**1**) and 2-phenyl-4-oxo-4H-chromene-3-carboxylic acid ethyl ester (**2**) with NaBH$_4$ at room temperature. The structure of novel derivatives of chromane has been revealed by ^{1}H NMR spectroscopic methods supported by DFT calculations and, in case of compound **3**, by X-ray crystallography.

2. Experimental section

2.1. General methods

All substances were used without further purification. Solvents for synthesis (methanol, acetone) were reagent grade or better and were dried according to standard protocols [11]. The melting points were determined using an Electrothermal 1A9100 apparatus and they are uncorrected. The IR spectra were recorded on a Pye-Unicam 200G Spectrophotometer in KBr. The ^{1}H and ^{13}C NMR spectra were registered in chloroform at 300 and 75 MHz, respectively, on a Varian Mercury spectrometer. The ^{1}H NMR

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Hydrocarbons as proton donors in C–H⋯N and C–H⋯S hydrogen bonds

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ABSTRACT

C–H⋯N and C–H⋯S hydrogen bonds were analyzed in complexes where acetylene, ethylene, methane and their derivatives are proton donors while ammonia and hydrogen sulfide are proton acceptors. Ab initio calculations were performed to analyze those interactions; MP2 method was applied and the following basis sets were used: 6-311++G(d,p), aug-cc-pVDZ and aug-cc-pVTZ. The results showed that hydrogen bonds for complexes with ammonia are systematically stronger than such interactions in complexes with hydrogen sulfide. If the fluorine substituted hydrocarbons are considered then F-substituents enhance the strength of hydrogen bonding. For a few complexes, mainly those where carbon atom in proton donating C–H bond possesses sp^3 hybridization, the blue-shifting hydrogen bonds were detected. Additionally, Quantum Theory of 'Atoms in Molecules' and Natural Bond Orbitals method were applied to analyze H-bond interactions.

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1. Introduction

There are different reasons why C–H⋯Y hydrogen bonds are the subject of numerous investigations [1]. First of all, such interactions were observed early on and compared with typical X–H⋯Y hydrogen bonds (X – proton donor, Y – proton acceptor) where both X and Y centers are electronegative atoms [2]. The above statement was proposed by Pauling as one of the characteristics of hydrogen bonding [3]. For C–H⋯Y interaction the proton donor is not an electronegative atom and hence there are numerous differences between typical X–H⋯Y interactions and C–H⋯Y ones [4]. However, there are also numerous similarities between them and that is why C–H⋯Y interactions are often classified as hydrogen bonds [4]. It was the subject of debates and disputes whether or not C–H⋯Y interactions could be classified as hydrogen bonds. The investigation of Taylor and Kennard is one of the most important ones supporting such an idea [5]. On the other hand, it was claimed that hydrogen bonding is an interaction without borders since very strong hydrogen bonds have the characteristics of covalent bonds whereas weak C–H⋯Y hydrogen bonds have the characteristics of van der Waals interactions [6].

While different criteria of the existence of hydrogen bonding were proposed and applied, it seems that the proton donating bond elongation, thus the weakening of this bond and the red-shift of the corresponding stretching mode is the strongest evidence of

hydrogen bonding formation [1,2]. However, unique interactions were found where an effect of the proton donating bond contraction was observed as a result of complexation and the corresponding shift of the stretching mode to the blue [7–9]. Hence those interactions were called inverse hydrogen bonds and further as blue-shifting hydrogen bonds, the latter name being most often used. It is worth mentioning that the contraction is usually observed for the C–H proton donating bonds and most often if C-atom is of sp^3 hybridization [9]. Sometimes other types of blue-shifting hydrogen bonds exist, these are N–H⋯Y, F–H⋯Y, P–H⋯Y or Si–H⋯Y [10–12]. However, the C–H bond contraction in C–H⋯Y interactions is much more common, which is another reason why C–H⋯Y interactions are the subject of numerous investigations.

There are different approaches aimed at explaining the nature of blue-shifting hydrogen bonding, focusing mainly on the reason of the X–H bond contraction as a result of complexation. For example, it was claimed that from the analysis of the electron charge density for H-bonded systems no differences could be seen between blue-shifting and red-shifting interactions [13]. The majority of other studies point out that there are differences between those two interactions. However, the NBO (Natural Bond Orbitals) approach was used to explain the nature of blue-shifting hydrogen bonding and it was stated that X–H bond length in X–H⋯Y system is controlled by two phenomena: X–H bond elongation due to $n(Y) \rightarrow \sigma^*(H–X)$ hyperconjugative interaction and the increase of polarization of X–H bond and its s-character [14]. Both effects are attributed to hydrogen bonding. However, the latter effect is responsible for the X–H bond contraction while the former one for its elongation.

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Thermal [2 + 3]-Cycloadditions of *trans*-1-Methyl-2,3-diphenylaziridine with C=S and C=C Dipolarophiles: An Unexpected Course with Dimethyl Dicyanofumarate

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The thermal reaction of *trans*-1-methyl-2,3-diphenylaziridine (*trans*-**1a**) with aromatic and cycloaliphatic thioketones **2** in boiling toluene yielded the corresponding *cis*-2,4-diphenyl-1,3-thiazolidines *cis*-**4** *via* conrotatory ring opening of *trans*-**1a** and a concerted [2 + 3]-cycloaddition of the intermediate (*E,E*)-configured azomethine ylide **3a** (*Scheme 1*). The analogous reaction of *cis*-**1a** with dimethyl acetylenedicarboxylate (**5**) gave dimethyl *trans*-2,5-dihydro-1-methyl-2,5-diphenylpyrrole-3,4-dicarboxylate (*trans*-**6**) in accord with orbital-symmetry-controlled reactions (*Scheme 2*). On the other hand, the reactions of *cis*-**1a** and *trans*-**1a** with dimethyl dicyanofumarate (**7a**), as well as that of *cis*-**1a** and dimethyl dicyanomaleate (**7b**), led to mixtures of the same two stereoisomeric dimethyl 3,4-dicyano-1-methyl-2,5-diphenylpyrrolidine-3,4-dicarboxylates **8a** and **8b** (*Scheme 3*). This result has to be explained *via* a stepwise reaction mechanism, in which the intermediate zwitterions **11a** and **11b** equilibrate (*Scheme 6*). In contrast, *cis*-1,2,3-triphenylaziridine (*cis*-**1b**) and **7a** gave only one stereoisomeric pyrrolidine-3,4-dicarboxylate **10**, with the configuration expected on the basis of orbital-symmetry control, *i.e.*, *via* concerted reaction steps (*Scheme 10*). The configuration of **8a** and **10**, as well as that of a derivative of **8b**, were established by X-ray crystallography.

1. Introduction. – Azomethine ylides, generated by different methods, were extensively explored in 1,3-dipolar cycloadditions aimed at the preparation of five-membered heterocycles. In many instances, the cycloadducts are important final products or building blocks for the synthesis of biologically active substances as well as in materials science [1–5]. Furthermore, the cycloadditions of azomethine ylides belong to the most frequently studied reactions used to test new catalysts for the stereocontrolled synthesis [6–8].

The oldest method for the generation of azomethine ylides consists in the thermal ring opening of properly substituted aziridines. The fundamental experiments by *Huisgen* evidenced the orbital control of this process [9]. Irrespective of the development of new methods, the thermal, conrotatory ring opening of aziridines is

Full Paper

Metallocarbonyl complexes of bromo- and dibromomaleimide: synthesis and biochemical application

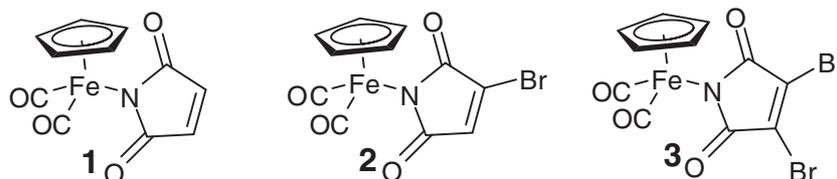# Bogna Rudolf,[a]* Michele Salmain,[b,c] Emilia Fornal[d,e] and Agnieszka Rybarczyk-Pirek[f]

Bromomaleimides react with cysteine residues to form thiomaleimides that can be further cleaved with TCEP (tris(2-carboxyethyl) phosphine) to regenerate the cysteine derivatives. Herein we report the preparation of new organometallic Fe complexes containing monobromo and dibromo maleimide ligands. Both of these complexes were characterised by X-ray diffraction. Organometallic bromomaleimide derivatives were reacted with the thiol-containing biomolecules: cysteine ethyl ester hydrochloride, glutathione and papain. These cysteine-containing molecules underwent a substitution reaction with metallocarbonyl bromo- or dibromo maleimide complexes, followed by an addition reaction to the thio-maleimide double bond if thiol was added in excess. The metallocarbonyl mono-bromomaleimide complex was shown to inhibit the peptidase activity of the enzyme papain. The resulting papain–maleimide product could be cleaved by addition of TCEP to regenerate the catalytically active enzyme. Copyright © 2012 John Wiley & Sons, Ltd.

Supporting information may be found in the online version of this article.

Keywords: metallocarbonyl complexes; papain inhibitors; biometalloorganic chemistry; bromomaleimides

Introduction

The maleimide motif is widely used for the selective alkylation of thiols in the pH 6.5–7.5 range and there are numerous N-functionalized maleimide reagents applied for cysteine modification.[1] Among these, $(\eta^5\text{-}C_5H_5)Fe(CO)_2(\eta^1\text{-}N\text{-maleimidato})$ **1** was applied as protein marker.[2,3] This metallocarbonyl complex displays characteristic strong absorption bands $\nu_{C=O}$, appearing

ligand substitution reactions with N-, S- or Se-containing residues of the enzyme target, as is the case for cysteine proteases inhibitors.[9] Alternatively, some substitutionally inert metal complexes were shown to act as enzyme inhibitors thanks to their particular scaffold, the metal centre creating a unique structural organization of the surrounding ligands in the 3D space. In this line, highly potent and specific ruthenium-based inhibitors have been identified for various protein kinases.[10]

in the 1950–2060 cm^{-1} mid-IR spectral region, which is usually free of any absorption of biomolecules or biological matrices. This feature made it useful as an IR-detectable marker to follow several biochemical processes as hormone–receptor or antigen–antibody interactions. Metallocarbonyl compounds including the maleimidato entity can be easily conjugated to bioactive compounds since they react with thiol groups in the presence of other functional groups in the biomolecules.[3–5]

More recently, we also reported that complex **1** and its molybdenum and tungsten analogues acted as irreversible inhibitors of the cysteine endoproteinase papain by irreversible alkylation of the sulfhydryl group present at its active site.[6] More generally, an increasing number of metal-based compounds have been shown to display enzyme inhibition abilities, with potential applications in medicine.[7,8] Some metal complexes with labile ligands were shown to act as enzyme inhibitors by

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Electron-density studies on hydrogen bonding in chromone derivatives. Part II: comparative study

**Magdalena Małecka · Lilianna Chęcińska ·
Carsten Paulmann**

Abstract The experimental electron density of a chromone derivative was determined from a multipole refinement of 100 K X-ray synchrotron data and complemented by theoretical calculations with experimental and optimized geometry. Atomic and topological properties were obtained using the Quantum Theory of Atoms in Molecules approach. The examination of topological parameters unambiguously showed π-delocalization within the H-bonded ring. The application of source function analysis confirmed the intramolecular N–H⋯O hydrogen bond to be a resonance-assisted hydrogen bond. The topological study confirmed the covalent nature of N–H⋯O interaction and the electrostatic nature of weak C–H⋯O interactions.

Keywords Electron density · Hydrogen bonding · Chromones · Source function · RAHB

Introduction

In this article, we describe the 100 K X-ray synchrotron accurate high-resolution molecular structure and charge-density analysis of 3(1-benzylamino-ethylidene)-chroman-2, 4-dione (*Mul_III*) (Fig. 1) as a continuing study of the crystal structures of chromone derivatives [1, 2] and the recent research on the electron-density (ED) distribution in this group of compounds [3, 4].

Our interest in the chromone family is twofold. First, we aim to understand the differences between electronic properties of the molecules that confer a wide range of biological activity [5, 6]. Second, we investigate the characters of the intramolecular and intermolecular hydrogen bonds observed in the crystal lattice.

For this reason, we present the experimental ED analysis of *Mul_III* as a continuation of our previous study [3] by a combined X-ray high-resolution diffraction study and high-level density functional theoretical calculations. We focused our attention on the crystal lattice packing and the arrangement of the intra- and intermolecular hydrogen bonds. The intramolecular hydrogen bond, which could be classified as a resonance-assisted hydrogen bond (RAHB), was analyzed in detail. It is generally believed that RAHB systems are accompanied by π-electron delocalization in the H-bonded rings (Fig. 1). Therefore, thanks to the possibility of using Bader's Quantum Theory of Atoms in Molecules (QTAIM) [7], we included detailed ED analysis to elucidate the intra- and intermolecular hydrogen bonding interaction in the investigated structure. The use of QTAIM theory allowed us to conduct a more detailed examination of the nature of the weak intermolecular interaction. In addition, the focus of this study was directed to the comparison of topological parameters with previously reported aspherical models of chromone structures.

We also evaluated the properties of the source function by Gatti and Bader [8], which was recently used to characterize hydrogen bonds. It has been shown that the character of the hydrogen bond is correlated with the sign of the contribution from the hydrogen, donor, and acceptor atoms [8].

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ORIGINAL RESEARCH

Modeling the electronic structure of formamide: an acid/base amphoteric solvent

Halina Szatyłowicz · Tadeusz M. Krygowski ·
Marcin Palusiak

Abstract H-bond formation of formamide, in which acidity centers interactions with fluoride ions and basicity centers with hydrofluoric acid, was used to determine its Lewis acidity and basicity. For this purpose, several methods and basis sets were tested, and the B3LYP hybrid functional in conjunction with a 6-311++G(d,p) basis set was selected as the one which gives high-quality results with reasonable computational requirements. Lewis acidity parameter (LAP) for the acidity center and Lewis basicity parameter (LBP) for the basicity center were determined as energies of the strongest H-bonds in the molecule. The obtained quantities, LAP $= -33.38$ kcal/mol and LBP $= -12.32$ kcal/mol, are in line with the empirical solvent parameters as Reichardt's E_T and Kamlet–Taft's basicity parameter β. Changes in the π-electron structure of the NCO fragment were observed as a result of H-bonding (HOMA in the range between 0.521 and 0.969) and can be easily explained with the contribution of resonance structures. Several QTAIM-based parameters allowed us to estimate such contributions and also to discuss the acid/base character of formamide. It was demonstrated that the complexation (via H-bonding) could be directly linked with a charge transfer (CT, data from both QTAIM and NBO) between the interacting fragments. It appeared that the QTAIM-based local properties of H-bonds were linearly correlated with CT, despite the fact that characteristics of the bonds formed by different atomic centers were used.

Keywords Formamide · Hydrogen bond · Lewis acidity · Lewis basicity · QTAIM · NBO

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Introduction

Solvent effects on chemical and biochemical processes as well as on physicochemical properties have been subject of a huge amount of works, which are nicely reviewed in an excellent monograph by Reichardt and Welton [1].The idea of amphoteric properties of aprotic solvents considered in terms of the Lewis acid/base theory was presented in the mid-1970s [2, 3] and is also associated with the linear solvation energy approach of Kamlet and Taft in which solvents are classified into solvents with H-bond acceptor basicities (HBA) [4] and such with H-bond donor acidities (HBD) [5]. The introduced HBA scale (called β scale) and HBD scale (called α scale) were based on the solvatochromic comparison of UV–Vis spectral data. The ideas are as follows. Normalized magnitudes of the enhanced solvatochromic band shift in HBA solvents are determined for 4-nitroaniline relative to N,N-diethyl-4-nitroaniline, and then $\Delta\tilde{v}$ is a numerical value in the β scale. The α scale, where the H-bond acceptor probe is a pyridinium-N-phenolate dye and

Spectroscopic and theoretical studies on some new pyrrol-2-yl-chloromethyl ketones

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A novel series of pyrrole-2-yl chloromethyl ketones were synthesized and studied by FT-IR, ^{1}H, ^{13}C NMR spectroscopy and DFT calculations at the B3LYP/6-311++G(d,p) level of approximation. Two stable conformations were detected in solution: s-*cis* and s-*trans* forms where the C=O group is located on the same side or the opposite side of N–H group, respectively. The conformational stability of these molecules is governed mainly by intermolecular hydrogen bonding interactions. The strength of hydrogen bonds was evaluated on the basis of ^{1}H chemical shift and infrared red shift $\Delta\nu_{\text{N–H}}$ of the stretching vibration of N–H proton donating bonds. The quantum theory of 'atoms in molecules' as well as the natural bond orbital method were applied to characterize hydrogen bonding interactions.

Introduction

Over the past few years some new carbonyl α-substituted pyrrole compounds have been investigated. Although the parent compound is experimentally well recognized[1] and has often theoretically analyzed,[2] little is still known about its derivatives and intra- and intermolecular noncovalent interactions within this group of moieties. At least, there are not many studies on interactions of such compounds. On the other hand, general studies show that intermolecular interactions strongly influence on the arrangement of molecules in crystals, especially directional hydrogen bonds.[3] It was also found that halogen bonds may be treated as counterparts of the latter interactions.[4] Recently, we have noticed the existence of C–Cl⋯O halogen bonds in crystal structure of 1-methylpyrrol-2-yl trichloromethyl ketone (**2**).[5]

We have analyzed other interactions of carbonyl α-substituted pyrroles, mainly different kinds of hydrogen bonds.[6] DFT calculations indicated that for the s-*cis* conformation of pyrrole-2-carboxylic acid, where N–H and C=O bonds are located at the same side of the moiety, two centrosymmetric dimers are possible.[6d] For each of them there are two equivalent hydrogen bonds. However in the first case these are two O–H⋯O bonds creating $R_2^2(8)$ motifs (graph-set-assignments) according to Etter's rules;[7] in the second case there are two N–H⋯O hydrogen bonds which form $R_2^2(10)$ motifs. These graph-set-assignments were introduced to H-bonded motifs existing in crystal structures.[7] R designates the ring and the number of atoms creating the ring is given in parentheses. Thus for $R_2^2(8)$ there are eight ring atoms linked through covalent and hydrogen bonds,

i.e. ⋯H–O–C=O⋯H–O–C=O⋯, since two hydrogen bonds exist between two carboxylic groups. The superscript and subscript designate the number of proton acceptors and proton donors, respectively. For $R_2^2(8)$ there are two equivalent proton acceptor O-centers (since the dimer is linked through two equivalent molecules) and two equivalent proton donating bonds (O–H). Etter has stated that there are also other motifs,[7] C designates the chain of atoms containing hydrogen bonding which repeats in the crystal structure, S concerns intramolecular hydrogen bonds and D corresponds to a dimer where there is a single hydrogen bond.

In the case of the s-*trans* conformer of pyrrole-2-carboxylic acid, there is only the possibility of the dimer containing two equivalent O–H⋯O bonds within the $R_2^2(8)$ motif. X-Ray measurement was performed on the crystal structure of pyrrole-2-carboxylic acid and it was found that s-*cis* conformers exist in crystals forming the $R_2^2(8)$ and $R_2^2(10)$ motifs mentioned above.[6e] The combined experimental thermochemical and computational study of 2-pyrrolcarboxylic acid and 1-methyl-2-pyrrolecarboxylic acid was performed very recently.[8] Another example is pyrrole-2-carboxamide analyzed by experimental spectroscopic and X-ray methods as well as by DFT calculations.[9] For the latter species, the s-*cis* conformer was detected and also the existence of centrosymmetric dimers in crystals connected through N–H⋯O bonds was indicated.

It is worth mentioning that for all α-substituted pyrrole compounds mentioned above different theoretical techniques may be applied to analyze various interactions. These are *ab initio* and DFT calculations which allow determination of the stable monomers' and dimers' molecular structures as well as their energies. Quantum theory of 'atoms in molecules' (QTAIM) is a useful tool to analyze those interactions since the characteristics of bond critical points (BCPs) often indicate the nature of the interactions considered.[10] It was found that there are mainly strong hydrogen bonds for α-substituted pyrrole compounds, especially if $R_2^2(8)$ motifs containing O–H⋯O hydrogen bonds are taken into account. This was found for centrosymmetric dimers of pyrrole-2-carboxylic

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Cyclooctatetraene in metal complexes—planar does not mean aromatic†

Justyna Dominikowska and Marcin Palusiak*

The cyclooctatetraene (COT) ring may act as an effective π-type ligand in metal complexes and very often in such complexes it adopts the planar structure, which in fact is not the most favourable conformation when compared with the free COT molecule. Such planarization is usually considered as an effect of COT ring aromatization due to charge transfer from the metal centre into the COT ligand and reorganization of the π-electron structure from a $4n$ to $4n+2$ Hückel system. In this paper it has been shown that the conformational changes of the COT ring, leading to its planarization and partial bond equalization, in the first order are connected with the complexation efficiency and not with the aromatization of COT itself. Such a conclusion was drawn on the basis of statistical analysis of X-ray data collected in the Crystal Structure Database (47 COT rings were taken into consideration, all found in the selected highest quality X-ray measurements) and advanced quantum-chemical calculations, including analysis of the electron density distribution made in the framework of *Atoms-in-Molecules Quantum Theory*.

Introduction

1,3,5,7-Cyclooctatetraene (COT) is a simple [8]annulene, C_8H_8. Being a $4n$ cyclic π-conjugated system, it is often considered as an example of a nonaromatic (or antiaromatic, when planar) species.[1] Both in the gas phase[2,3] and crystal state[4] COT adopts a tub-like conformation (D_{2d} symmetry) with clearly localized single and double bonds of 1.47 Å and 1.33 Å length, respectively. This closed-shell nonplanar structure is accompanied by a chemical behaviour being characteristic of conjugated alkenes.[5] The process of planarization of tub-shaped COT was investigated and it was found that the planar structure can be forced, for instance, by annelation with rigid bridges leading to geometric constrains that result in bond delocalization in the COT ring.[6–8] Planarization of COT can also be reached by a partial rehybridization at the carbon atom due to a forced decrease of the HCC bond angles at carbon atoms forming the double bond.[9] However, it should be emphasized that the analysis of ring currents of COT derivatives planarized in various ways clearly showed that planarization in these cases has nothing in common with aromatization.[10,11] For a very recent review on theoretical and experimental studies regarding the planar COT structure see ref. 12. It was also reported that the COT ring exhibits a very unusual electron-density topology resulting from specific orbital overlapping in the tub-like conformation.[13] It was found that this through-space orbital interaction is mostly connected with exchange repulsion between filled p-type orbitals centred on oppositely placed carbon atoms. The substituent effect in COT was also investigated by means of computational methods.[14,15]

The efficient electron affinity of COT is well known and it has been frequently reported that COT forms a stable dianionic structure, for instance in the presence of electron-donating alkali[16–19] and some transition metals.[20–23] However, although it was repeatedly reported that COT forms stable complexes with transition metals and that in many such complexes it adopts a dianionic aromatic form (with $4n+2$ π-electrons), the isolated dianion COT^{2-} itself has a very short lifetime,[24] which indicates a relatively low kinetic stability of that species. The COT^{2-} lifetime is 6 fs, which is drastically short as compared with, for instance, 260 and 6500 fs for C_4^{2-} and CO_3^{2-}, respectively.[24]

The COT ring formally possesses four bonds of π-type (double CC bonds in free COT), thus it is an effective π-type ligand. What is interesting, as a ligand it exhibits the whole conformational spectrum—from tub-like up to planar structure—and different coordination modes, *i.e.* η^2, η^4, η^6 and η^8.[16,25–31] Therefore, an essential conformational variety of the COT ring can be observed for metal complexes. These changes in conformational properties are often considered as the result of charging of the COT ring and in consequence full or partial aromatization of that ring ($4n$ π-electron structure in COT *vs.* $4n+2$ π-electron structure in its dianion).

Since such an essential conformational variety of COT can be observed for metal complexes, we decided to check if there is any direct relationship between COT conformation and its aromatic character. For the purposes of our studies we analyzed experimental data collected in the Crystal Structure Database.[32] Additionally, selected molecular systems found in the CSD were chosen for more detailed computational studies.

Methodology

Crystal structure database searching

The search through CSD[32] (release 2009) was done in order to collect selected data for further analysis. The presence of an unsubstituted COT ring in the crystal structure was the main criterion of the search. Additionally, the search was limited to data derived from high-quality X-ray measurements ($R \leq 0.075$). Crystal structures with errors, disordered structures, powder

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† Electronic supplementary information (ESI) available: CSD refcodes, results of population analysis, geometries and total energies of the systems studied. See DOI: 10.1039/c0nj00060d

NJC

PAPER

The effect of benzoannulation on the transition state and the proton transfer equilibrium in di(2-pyridyl)methane derivatives†‡

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The tautomeric properties of di(2-pyridyl)methane and its benzoannulated derivatives were studied using a computational approach (M05/6-31G(2d,p)). Our analysis showed that the degree of cyclic π-electron delocalization in benzene and pyridine rings is directly connected to the effect of resonance present in quasi-rings formed by intramolecular hydrogen bonds of the N–H···N type. This direct relation can be explained using two concepts, namely, the concept of Clar's aromatic sextet and the Leffler–Hammond concept originally developed for the explanation of the energy relation between ground-state and transition-state structures corresponding to proton transfer in H-bridges. Application of these two different concepts allows us to explain in detail the role of intramolecular hydrogen bonding in polycyclic aromatic hydrocarbons containing N heteroatoms.

Introduction

Stepwise benzoannulation to benzene allows one to construct a huge number of benzenoid hydrocarbons. They present a great variety of physicochemical properties,[1–4] which are mostly dependent on the mobile nature of the π-electron structure and π-electron delocalization.[5–9] Analyses of resonance energy-like characteristics describing whole molecules show a great diversity in this property,[10,11] with even similar molecules, such as tetracene and its isomers,[12] differing in energy by 14 kcal mol^{-1}. It is important to mention that diversity in π-electron delocalization observed in individual rings of a given benzenoid hydrocarbon is sometimes very large, with systems ranging from antiaromatic to fully aromatic. This has been shown using various measures of π-electron delocalization (generally known as aromaticity indices).[10,13–26] The references mentioned lead to the well-documented conclusion that rings in a given molecule of a benzenoid hydrocarbon may have strongly different π-electron delocalization. To some degree,

it may be said that, depending on the kind of benzoannulation (*i.e.* how many rings are annulated and in what position), the parent ring may have substantially different π-electron properties. Consider a very simple example: two rings are annulated to the benzene ring (denoted, say, by A), on both sides of A. As a result we obtain anthracene or phenanthrene with A in a central position. We see that π-electron delocalization in ring A in both cases differs substantially. In the phenanthrene molecule the ring A has a localized double bond and its aromaticity is much lower than in two lateral rings, whereas in anthracene all rings have comparable aromatic characters, as shown by values of different aromaticity indices.[27,28] The problem of the mode of benzoannulation in this case is also associated with specific features. Greater stability is observed for kinked linear polyacenes rather than for straight linear ones, as shown recently for phenanthrene and anthracene,[29] and even for infinite chains of these two kinds of systems.[30] It was also shown recently[31–34] that if the annulated ring is not a benzene but the so-called quasi-aromatic ring in which CHCHCH fragment is replaced by O–H–O or O–Li–O fragments (or similar), then these quasi-rings function in a similar way as the benzene rings, being more similar in the case of O–Li–O and less similar for O–H–O.

The purpose of this paper is to investigate how the quasi-ring formed as a result of H-bond in two positions of proton location depends on the kind of benzoannulation to the pyridine ring participating in H-bond complexation. We also consider how the location of the proton in the transition state (TS) depends on the aromaticity of both the π-electron system participating in the H-bond and the opposite relation – how the hetero-ring and the complete π-electron moieties depend on the position of

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organic compounds

2-Methoxy-3-[(3,4,5-trimethoxyanilino)-methylidene]-3,4-dihydro-2H-1-benzo-pyran-4-one

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The title molecule, $C_{20}H_{21}NO_6$, adopts a keto–amine tautomeric form. An intramolecular N—H···O hydrogen bond, classified as a resonanse-assisted hydrogen bond, influences the molecular conformation; the two benzene rings form a dihedral angle of 24.6 (1)°. In the crystal structure, weak intermolecular C—H···O hydrogen bonds link molecules into chains propagating along [001].

Related literature

For the biological propertties of similar structures, see: Khan *et al.* (2009). For related structures, see: Gilli *et al.* (1994); Bertolasi *et al.* (1998); Małecka & Budzisz (2006); Małecka (2007).
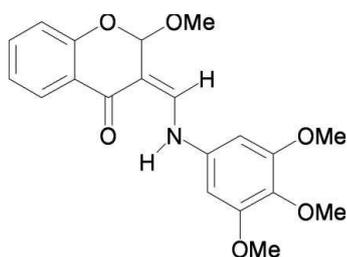
Experimental

Crystal data

$C_{20}H_{21}NO_6$ M_r = 371.38

Monoclinic, $P2_1/c$
a = 11.6145 (6) Å
b = 20.8689 (9) Å
c = 7.3728 (5) Å
β = 94.533 (5)°
V = 1781.44 (17) Å³

Z = 4
Cu $K\alpha$ radiation
μ = 0.86 mm⁻¹
T = 100 K
0.2 × 0.05 × 0.03 mm

Data collection

Oxford Diffraction Gemini E Ultra diffractometer
Absorption correction: multi-scan (*CrysAlis RED*; Oxford Diffraction, 2009)
T_{min} = 0.844, T_{max} = 1.000

7511 measured reflections
2862 independent reflections
2344 reflections with $I > 2\sigma(I)$
R_{int} = 0.024
Standard reflections: 0

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.037
$wR(F^2)$ = 0.101
S = 1.05
2862 reflections

248 parameters
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.38 e Å⁻³
$\Delta\rho_{min}$ = −0.22 e Å⁻³

Table 1
Hydrogen-bond geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1···O4	0.88	2.00	2.661 (2)	131
C14—H14A···O4^i	0.98	2.48	3.414 (2)	160

Symmetry code: (i) $x, -y + \frac{1}{2}, z - \frac{1}{2}$.

Data collection: *CrysAlis CCD* (Oxford Diffraction, 2009); cell refinement: *CrysAlis RED* (Oxford Diffraction, 2009); data reduction: *CrysAlis RED*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *PLATON* (Spek, 2009); software used to prepare material for publication: *PLATON*.

Supplementary data and figures for this paper are available from the IUCr electronic archives (Reference: CV2678).

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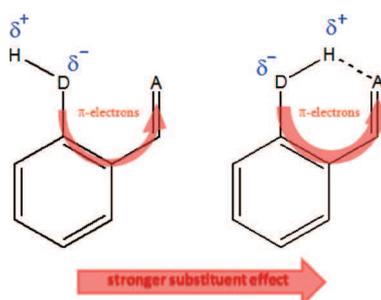
H-Bonding-Assisted Substituent Effect[†]

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In this paper we investigate the influence of intramolecular noncovalent interaction, i.e., H-bonding and Li-bonding, on the properties of substituents communicating through the resonance (mesomeric) effect in such molecular systems as salicylaldehyde, *o*-hydroxy Schiff base, *o*-nitrosophenol, and their lithium analogues. The investigated systems are usually considered as molecular patterns of intramolecular resonance-assisted hydrogen bonds (or its analogues in the case of Li-bonded systems). We show that the relation between intramolecular noncovalent interactions, $A-H\cdots B$ and $A-Li\cdots B$, and the π-electron delocalization in the sequence of π-conjugated covalent bonds linking A and B can be considered in terms of the Hammett-like substituent effect in which electron-donating and electron-withdrawing properties of substituents are affected by the noncovalent interaction.

Introduction

Hydrogen bonding is one of the most important interactions since it is responsible for most processes in the bio- and geospheres as well as playing an important role in the development of new materials.[1−8] In the past two decades

Gilli et al.[9−17] introduced a concept of resonance-assisted hydrogen bonding (RAHB) in which H-bonding strength is related to the π-electron delocalization in the spacer between the proton-donating -AH group and a proton-accepting -B group in $R^1A-H\cdots BR^2$. In a particular case, when R^1 and R^2 are linked covalently, the H-bond is the intramolecular one. According to Gilli's concept of RAHB, a mechanism of synergetic interplay is assumed between the resonance of π-electrons in the spacer and the H-bond formation. Undoubtedly, the electronic properties of -AH and -B groups interacting via intramolecular H-bonding change in comparison with their states before interaction.[18] The consequences of

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[†] Dedicated to our friend Profesor Gastone Gilli (University of Ferrara, Italy) in recognition of his remarkable contribution to the field of research on hydrogen bonding.

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X–H⋯π and X–H⋯N hydrogen bonds – Acetylene and hydrogen cyanide as proton acceptors

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ABSTRACT

The hydrogen-bonded systems were considered where acetylene or hydrogen cyanide acts as a proton acceptor and different proton donating molecules are taken into account. The B3LYP/6-311++G(d,p) and MP2/6-311++G(d,p) calculations were performed for the systems considered; for HCN⋯HF and C_2H_2⋯HF complexes various levels of approximation were applied up to CCSD(T)/6-311++G(3df,3pd)// CCSD/6-311++G(3df,3pd). The Quantum Theory of "Atoms in Molecules" (QTAIM) was also applied. It was found that π-electrons of acetylene might act as the proton accepting centers and the found complex conformations are T-shaped ones. For hydrogen cyanide molecule the nitrogen atom acts as the proton acceptor center but not π-electrons. The characteristics of the bond critical points were also considered for the analyzed interactions and numerous correlations were found between geometrical, energetic and QTAIM parameters. The decomposition of the interaction energy for the systems analyzed was also applied.

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1. Introduction

There are numerous studies on X–H⋯π interactions which are often classified as hydrogen bonds since π-electrons may be treated as proton acceptors (X–H designates the proton donating bond) [1]. There are also other characteristics of such systems which are similar to the characteristics found for typical hydrogen bonds, as for example, for O–H⋯O interactions [1]. Hence the X–H⋯π interactions have been a subject of extensive investigations, and their meaning for various chemical, physical and biochemical processes was worked out in recent and earlier studies [1,2]. In many cases those interactions were found to affect the arrangement of molecules in crystals, even C–H⋯π interactions (often designated as CH/π [3]) were detected in numerous systems. The latter interactions are important in crystal structures since C–H bonds and π-electronic systems (often aromatic systems) are common in crystals of organic and metal–organic compounds. However, O–H⋯π, N–H⋯π and other X–H⋯π interactions were detected and analyzed in numerous studies [1].

The T-shaped structures of C_2H_2⋯HX complexes were investigated early on from the experimental [4,5] as well as theoretical [6,7] points of view. A deeper analysis of the nature of H⋯π interaction was performed [8] since QTAIM analysis [9] was applied as well as various complexes that formed between hydrogen fluoride

and π-systems were analyzed. The following proton acceptors were taken into account in the latter study: acetylene, ethylene, cyclopropene, cyclobutadiene and benzene and in all cases studied a bond critical point (BCP) was found between the H atom of the hydrogen fluoride and the CC π-bond. It is worth noting that the BCP is situated on the bond path connecting the H-atom attractor and the BCP of the mentioned CC π-bond [8]. There is another early interesting study on H-bonded systems where the acetylene molecule is the proton acceptor and there are the following proton donors: HF, HCl, HCN, HNC and HCCH [10]. These are the T-shaped complexes where there is the π charge transfer of the C≡C bond to the σ* antibonding orbital of H–X [10].

The T-shaped dimer of acetylene is one of the model systems for which calculations at different levels of approximation were carried out in numerous studies [11,12]. The binding energy for such a complex calculated at MP2/6-311++G(d,p) level of approximation is equal to −1.1 kcal/mol. However, when considering other T-shaped complexes where acetylene is the proton acceptor and there are the following proton donating species: HCN, HCl and HF then these energies amount to −1.8, −1.9 and −3.1 kcal/mol, respectively [11]. The decomposition of interaction energy according to the Morokuma approach [13] was performed for the above-mentioned T-shaped complexes [11] and it was found that not only electrostatic but also other attractive interaction energy terms are important and responsible for the stability of these systems. For the FH⋯C_2H_2 complex the decomposition of binding energy is as follows: exchange (EX), electrostatic (EL), polarization (PL), charge transfer (CT) and correlation (CORR) terms are equal to: +6.3,

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Basis Set and Method Dependence in Quantum Theory of Atoms in Molecules Calculations for Covalent Bonds

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The influence of various small- and medium-size basis sets used in Hartree−Fock (HF) and density functional theory (DFT)/B3LYP calculations on results of quantum theory of atoms in molecules based (QTAIM-based) analysis of bond parameters is investigated for several single, double, and triple covalent bonds. It is shown that, in general, HF and DFT/B3LYP methods give very similar QTAIM results with respect to the basis set. The smallest 6-31G basis set and DZ-quality basis sets of Dunning type lead to poor results in comparison to those obtained by the most reliable aug-cc-pVTZ. On the contrary, 6-311++G(2df,2pd) and in a somewhat lesser extent 6-311++G(3df,3pd) basis sets give satisfactory values of QTAIM parameters. It is also demonstrated that QTAIM calculations may be sensitive for the method and basis set in the case of multiple and more polarized bonds.

Introduction

As opposed to the wave function quantum mechanics, the quantum theory of atoms in molecules (QTAIM) introduced by Bader[1−6] gives the opportunity to have an insight into a region of a system. This opportunity meets the interest of most of chemists who wish to have a theoretical tool to study a small part of a molecule only, instead of dealing with the total energy of a whole system. Nowadays QTAIM is a very powerful method in investigating inter- and intramolecular interactions.[7−13]

In the QTAIM approach a system is divided to subsystems by means of a *physically well-defined* surface which is established in such a way that there must not be a flux in the electron density gradient vector field ($\vec{\nabla}\rho$) through the surface. Following the gradient vector of ρ from some initial point one terminates at a critical point (CP), a point where $\vec{\nabla}\rho = \vec{0}$. Of particular interest is a critical point in which the electron density is a minimum with respect to the direction of a line connecting two nuclei and a maximum with respect to all directions perpendicular to this line, thus being a saddle point with the $(3,-1)$ curvature. A critical point with such characteristics is called a bond critical point (BCP). BCPs are of particular interest since they can be used in the recognition of chemical bonds between atoms and then in studies of the character of these interatomic interactions.

Most of QTAIM calculations are performed with the use of rather small basis sets. Therefore, one may ask about the dependence of values of QTAIM parameters on both the basis set and the method used in QTAIM calculations, i.e., about the stability of values of QTAIM parameters with respect to the change of both the basis set and the method used in QTAIM calculations. The present paper is a continuation of our recent studies[12] of this issue. Previously, we were investigating hydrogen bonds of the CH···N type.[12] In this paper we investigate several covalent bonds, which can be grouped into either single, double, or triple or either nonpolarized or polarized.

Methodology

To study the stability of QTAIM calculations with respect to the basis set and the method, we chose several small molecules possessing single, double, and triple covalent bonds: (i) ethane (H_3C-CH_3), fluoromethane (H_3C-F), and methanol (H_3C-OH), (ii) ethene ($H_2C=CH_2$) and formaldehyde ($H_2C=O$), (iii) acetylene ($HC\equiv CH$), nitrogen molecule ($N\equiv N$), and hydrogen cyanide ($HC\equiv N$), where in parentheses we indicated the bond of interest, i.e., that one for which BCP's values of QTAIM parameters were computed. Geometry optimizations of studied molecules have been performed at the B3LYP/aug-cc-pVQZ level of theory. However, it should be mentioned that in fact any other method could have been used for the geometry optimization since the aim of these studies was to compare values of QTAIM parameters obtained by means of different approximations for a system with the same geometry, whatever the source of the geometry is.

Various QTAIM parameters which are commonly used in the description of chemical bonding were then computed using a large set of basis sets of Pople[14] and Dunning[15,16] type. Small-size basis sets of Pople type have also been used in these studies since their use may be the only option in the case of much more time-consuming calculations, e.g., for very bulky molecular systems. Results obtained by means of Pople-type basis sets (or the smallest DZ-quality of Dunning type) will also be compared to those obtained by means of more reliable[12] cc-pVTZ and particularly aug-cc-pVTZ basis sets. In the present calculations we do not use Dunning-type basis sets with the cardinal number larger than 3 (TZ) since the wave function file (wfn) is not generated if the angular momentum quantum number *l* is greater than 3; i.e., there is a technical limitation for the usage of *f*-type Gaussian-type orbitals. In our recent studies of QTAIM stability for the CH···N hydrogen bond[12] we have also used d-aug-cc-pVTZ as well as cc-pVQZ and aug-cc-pVQZ basis sets with *g*-functions removed in the case of

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Nature of a Hydride−Halogen Bond. A SAPT-, QTAIM-, and NBO-Based Study[§]

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Ⓢ *Supporting Information*

ABSTRACT: The nature of a hydride−halogen bond is investigated by means of high-level quantum mechanical calculations expended with symmetry-adapted perturbation theory (SAPT), quantum theory of atoms in molecules (QTAIM), and natural bond orbital (NBO) methods. As model hydride−halogen bonded systems complexes between either LiH or HBeH and either XCF_3 or XCCH (X = F, Cl, Br, I) are used. It is shown that the formation of a hydride−halogen bond leads to the elongation of the $R^{\delta+}−H^{\delta−}$ hydride bond, which is accompanied by the blue shift of the $\nu_{R−H}$ stretching vibration frequency and the increase of the IR intensity of this mode. All these effects, although untypical in the case of, e.g., hydrogen bonds, can be considered as rather typical for hydride−halogen bonded systems. The decomposition of the interaction energy based on the SAPT method clearly indicates the dominant role of the induction term, thus the inductive nature of a hydride−halogen bond in opposition to previous findings. NBO-based analysis indicates the charge transfer from the hydride molecule to the more remote parts of the halogen donor and that the elongation of the R−H bond is caused by the charge outflow from the σ_{RH} bonding orbital.
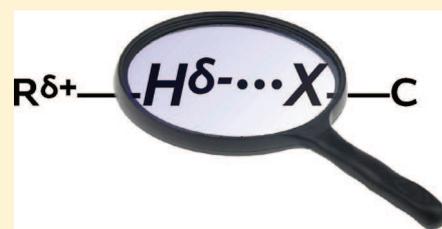
■ INTRODUCTION

In the plethora of inter- and intramolecular interactions the so-called halogen bonds have recently found a great interest.[1−30] These are defined as interactions between a halogen atom (X) and an atom with an excess of electron charge density, most often being an atom with the electron lone-pair (Y). Thus they may be denoted by the $R_X−X\cdots Y−R_Y$ formula. At first, the interaction of this type may seem to be surprising because the halogen atom, being highly electronegative, should accumulate the negative charge and then, as a result, lead to the repulsive interaction while acting on Y. Thus any stabilizing interaction of the $R_X−X\cdots Y−R_Y$ type should not exist if one considers an atom in a molecule as a center bearing entirely positive or entirely negative charge only. The explication is in the anisotropy of the electron density distribution around the halogen atom.[4,5,13,14,24,31] Namely, it is accepted that the electron density distribution around the halogen atom accepts ellipsoidal shape with longer radius being perpendicular to the direction of the $R_X−X$ halogen bond.[4,5,13,14,24,31] As a result a region of the positive electrostatic potential (the so-called σ-hole) is formed on the outermost portion of the halogen's surface along the $R_X−X$ bond's direction. More precisely, the term σ-hole was originally referred to the electron-deficient outer lobe of the p (or nearly p) orbital involved in the formation of the $R_X−X$ covalent bond.[4,5,13,14] This σ-hole is then encompassed by the negative electrostatic potential that forms an areola-like belt around the central part of X.[4,5,13,14,24] In this way the halogen bond is a consequence of the interaction between Y and the σ-hole region of X and is believed to be mainly of the electrostatic nature.[6,11,17,27] However, the dominant role of other energy contributions was also indicated.[11,17,28] Riley and Hobza have

found that the dispersive interaction may be dominant in the interaction energy of $H_3CX\cdots OCH_2$ (X = Cl, Br) systems.[17] However, this finding relates to rather untypical halogen bonded systems where $R_X = H_3C$ and the halogen atom is small. Otherwise, the electrostatic contribution prevails the interaction energy[17] of a halogen bond. On the other hand, the significantly covalent nature of halogen bonds due to the dominant HOMO/LUMO charge transfer has very recently been shown.[28] In reverse to what was claimed by Riley and Hobza, the electrostatic contribution is to be systematically overbalanced by the exchange repulsion.[28] Furthermore Zou et al.[11] have found the dominant role of charge transfer in dihalogen$\cdots NH_3$ type systems, whereas the dominance of electrostatic term has been found if the halogen was bound to a carbon.

Investigating the halogen bond as resulting mainly due to the electrostatic interaction between the σ-hole of a halogen atom and an atom with an excess of electron density, e.g., the electron lone-pair, the interaction between partially negatively charged hydrogen atom and halogen, $R−H^{\delta−}\cdots X−R_X$, should also exist. Indeed, this hydride−halogen bond is known and has already been investigated earlier for a small group of representative model systems.[32,33] Very recently it has also been shown that a partially negatively charged hydrogen atom can readily interact with an atom with the electron lone-pair vacancy, leading to the so-called charge-inverted hydrogen bonds.[34−36] Both these examples show that $H^{\delta−}$ behaves as a good Lewis base.

Electron density studies on hydrogen bonding in two chromone derivatives

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The experimental electron densities of two chromone derivatives have been determined from X-ray synchrotron diffraction data at low temperature (100 K). Topological analysis of the electron density has been used to analyze the formation of resonance-assisted hydrogen bonds (RAHBs). Geometrical and topological parameters confirm π-electron delocalization within the hydrogen-bonded ring. In addition, weak $C-H\cdots O$ interactions were identified in both structures. Hydrogen-bond energies allowed medium and weak hydrogen bonds to be distinguished.

1. Introduction

Ultra-high-resolution X-ray charge density experiments provide information on the precise electron density distribution (EDD) as a helpful tool for characterizing the electronic properties of bonding and non-bonding interactions (Koritsanszky & Coppens, 2001). Bader's approach of 'Atoms in Molecules' (AIM; Bader, 1990) allows a topological analysis of $\rho(\mathbf{r})$, yielding a quantitative description of atoms, bonds and non-bonding interactions. Experimental EDD can be derived using the Hansen–Coppens multipolar atom model (Hansen & Coppens, 1978), which is used in the multipole refinement of high-resolution X-ray diffraction data.

In this paper experimental methods were applied to derive a charge density distribution for two chromone derivatives. Bader's AIM approach was used to analyze the experimental EDD as part of ongoing investigations. Research on chromone and coumarin derivatives has been stimulated by their promising pharmacological, analytical and agrochemical applications (Rosskopt *et al.*, 1992; Ohemeng *et al.*, 1993; Kostova, 2007; Musa *et al.*, 2008). Alkylating properties of these compounds have been extensively investigated and widely described in many papers (Budzisz *et al.*, 2002, 2003; Kulkarni *et al.*, 2006; Przybylski *et al.*, 2009; Asmah Susidarti *et al.*, 2009). Owing to their ability to coordinate metal ions, transition metal complexes with chromone as well as coumarin derivatives show significant biological activity and they are the subject of current research (Grazul & Budzisz, 2009).

The experimental charge densities of 3-(aminophenylmethylene)chroman-2,4-dione (I) and the compound 3-(methylaminophenylmethylene)chroman-2,4-dione (II) [see (I) and Fig. 1] were determined. Our main interest is in the intramolecular hydrogen bond which closes an extra six-membered hydrogen-bonded ring and is common to both compounds. Homonuclear resonance-assisted hydrogen bonds (RAHBs) have been subjected to a charge density study before (Madsen *et al.*, 1998). With respect to the geometrical parameters within this heteronuclear $O=C-C=C-N-H$ keto-amine ring the $N-H\cdots O$ interaction can be classified as

Electronic properties of two adjacent intramolecular hydrogen bonds and their effects to the molecular charge distribution: Experimental synchrotron microcrystal and DFT computational study

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A R T I C L E   I N F O

A B S T R A C T

The experimental crystal structure and corresponding theoretical electron density determination of 2-hydroxy-4,4-dimethyl-6-oxo-cyclohex-1-ene carboxy amide is reported with special focus on two adjacent intramolecular hydrogen bonds (O–H⋯O and N–H⋯O). The possible tautomeric forms are studied and their theoretical populations in the gas phase were determined. Additionally, theoretical models which refer to the title compound were optimized and investigated in terms of the combined analysis of ED-topology, energy densities, electron localizability indicator (ELI), delocalization index and source function (SF). This analysis confirmed the O–H⋯O interactions to be resonance assisted and of medium strength, while the N–H⋯O interactions are rather weak. Moreover, in all cases the hydrogen bond strength and amount of resonance in the six-membered rings is related to the type of interaction (O–H⋯O and/or N–H⋯O) and to the molecular symmetry.

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1. Introduction

Intramolecular hydrogen bonds and their crucial role in biological chemistry have been reported in the literature [1]. Mostly, intramolecular hydrogen bonds are part of planar six-membered rings stabilized by a conjugated π-system. The structure and electron density determination of the title compound, (I) that includes two adjacent intramolecular hydrogen bonds have been reported. Our research has been recently focused to this topic using experimental and computational methods [2,3]. It turned out that in such systems π-electron delocalization appears in H-bonded rings, which entails a change in the geometrical and topological parameters [4]. Thus, the intramolecular hydrogen bonds were regarded as resonance-assisted hydrogen bonds (RAHB). In this work we focus on systems that exhibit two intramolecular hydrogen bonds in adjacent six-membered rings. How does the presence of two adjacent hydrogen bonds affect the geometrical and topological parameters? The known compound (I) is almost a prototypical example for systems with a O–H⋯O and a N–H⋯O hydrogen bond. It was prepared following a synthesis known from literature [5]. A similar moiety of two adjacent strong intramolecular hydrogen

bonds was examined by Bertolini et al. [6]. Due to their biological relevance and pharmacological activity series of related compounds with a hydroxy group in *cis* conformation to an amidic moiety were investigated [7,8].

However, the crystal structure of (I) has not been elucidated yet. Unfortunately, only very small crystals were obtained. Because of the weak diffraction, data collection was carried out at the synchrotron beamline F1 at Hasylab/DESY. The crystal structure determination reveals the favored tautomeric form in the crystal lattice and what factors stabilize it. In order to investigate in detail the double intramolecular hydrogen bond formation, six optimized structures of smaller model compounds were compared in terms of Quantum Theory of Atoms in Molecules (QTAIM) [9], electron localizability indicator (ELI) [10], source function (SF) [11], and delocalization index (DI) [12].

2. Results and discussion

2.1. Crystal structure

Compound (I) crystallizes in the monoclinic space group P2₁/c. The molecular structure is shown in Fig. 1. The cyclohexene ring (ring 'c') adopts a slightly distorted half-boat conformation with an apical C4 atom. The puckering parameters [13] are: $Q_T = 0.449(2)$ Å, $\varphi_2 = 4.2(2)°$, $\theta_2 = 129.0(2)°$. The remaining non-

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Cyclooctatetraene Dianion—An Artifact?

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Abstract: Cyclooctatetraene in its dianionic form (COT^{2-}) is considered to be partially or fully aromatic due to the fact that, unlike its neutral counterpart, it adopts planar structure with CC bonds equalized. However, some authors report that this dianion is neither planar nor aromatic. Thus, we performed a detailed analysis of the COT^{2-} case. The influence of several technical parameters on the result of calculations on COT^{2-} was investigated. It appears from our analysis that the use of some specific level of approximation may lead to very misleading results in which the COT ring occurs in its neutral structure, in fact being neither planar nor aromatic. Additionally, our results may suggest that COT^{2-} dianion is rather an artificial structure (being the result of specific basis set description) and should not occur in experimental conditions.

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Key words: cyclooctatetraene; dianion; aromaticity; antiaromaticity; HF; MP2; DFT; QTAIM; basis set; diffuse functions

Introduction

Annulenes, being simple monocyclic polyenes, belong to a group of fundamental chemical species in organic chemistry.[1] This group of compounds is often named as [n]-annulenes where n denotes the number of carbon atoms. Thus, we have [6]-annulene, generally known as benzene, and [4]-annulene and [8]-annulene, known as cyclobutadiene and cyclooctatetraene, respectively. The structure of the given annulene greatly affects the chemical and physical properties of that chemical species. For instance, the n number is directly related to Hückel's rule, and, thus, some annulenes are fully aromatic (with benzene being the aromatic molecule archetype) and some are antiaromatic, for example, the cyclobutadiene or cyclooctatetraene (COT) in planar conformation. Unlike cyclobutadiene and benzene, the unsubstituted COT ring adopts a nonplanar structure with D_{2d} symmetry.[2,3] (See Fig. 1 for graphical representation.) This is due to the ring strains acting in COT, which lead to a tub-like conformation with clearly localized character of its π-electron structure. Thus, COT in its ground-state geometry reflects the structure being typical of nonaromatic Hückel's $4n$ π-electron systems. These structural characteristics are accompanied by chemical behavior typical of conjugated alkenes.[1]

Very recently, it was reported that COT in its ground-state structure also exhibits a very unusual electron density topology, with a set of two ring critical points (RCPs) and one cage critical point instead of a single RCP. This unusual topology of the electron density is directly connected with the COT tub-like con-

formation and the through-the-space p-type orbital overlapping leading to partial charge concentration above and below the ring mid-plain.[4] Because COT consists of a sequence of conjugated formally single and double CC bonds, it may act as a medium in π-electron interaction between substituents. Therefore, the substituent effect was also investigated for simple COT derivatives.[3,5]

Planarization of the COT ring was a subject of several studies. It was found that the planar structure of COT can be reached by the annelation with rigid bridges leading to geometric constrains that result in bond delocalization in the COT ring.[6–8] Planarization of COT can also be reached by a forced decrease of the HCC bond angles at carbon atoms forming a double bond.[7] It should be pointed out that the analysis of ring currents of COT derivatives planarized in various ways clearly showed that in fact such planarization does not lead to COT aromatization.[9,10] It is remarkable that planar COT rings can also be found in metal complexes.[11–19]

ORIGINAL RESEARCH

DFT studies and AIM analysis of intramolecular N–H···O hydrogen bonds in 3-aminomethylene-2 methoxy-5,6-dimethyl-2-oxo-2,3-dihydro-2λ^5-[1,2]oxaphosphinin-4-one and its derivatives

Magdalena Małecka

Abstract The intramolecular N–H···O hydrogen bonds in 3-aminomethylene-2 methoxy-5,6-dimethyl-2-oxo-2,3-dihydro-2λ^5-[1,2]oxaphosphinin-4-one and its derivatives (F, H, Li, -BeH) were studied by DFT (density functional theory) methods. The results of calculations were obtained at B3LYP/6-311++G(d,p) level on model species, with the resonance-assisted hydrogen bonds (RAHB). Topological parameters such an electron density, its Laplacian, kinetic electron energy density, potential electron energy density, and total electron energy density at the bond critical points (BCP) of H···O/N–H contact bonds from Bader's 'Atoms in molecules' (AIM) theory were analyzed in details. The energy of the N–H···O interactions studied here was found rather weak ($E_{HB} = 2.53–12.08$ kcal/mol). The results of AIM ellipticity indicated π-delocalization over all six atoms within ring.

Keywords Hydrogen bond · Resonance-assisted hydrogen bonds · DFT calculations · The Bader theory · Bond critical point · Ellipticity

Introduction

Hydrogen bond systems are one of the key interactions that determine the structure, functionality, and dynamic processes in a large variety of systems. Hydrogen bonds

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frequently occur in inorganic, organic, and biological chemistry. Therefore, the understanding and comprehensive studies of the nature of hydrogen bonds is underpinning any insight into molecular bases of chemical and biological systems [1–3].

Aminophosphonic acids are synthetic analogs of natural amino acids in which the carboxylic group is replaced by the phosphonic acid group. Numerous aminophosphonic acids, their esters, and salts have attracted special attention due to their synthetic and biological value both as agrochemical (herbicides, pesticides, and growth regulators in plants) and medical (antibiotics, antivirals, and enzyme inhibitors) products with wide applications [4–7]. Fosmidomycin [HCON(OH)–(CH$_2$)$_3$–PO$_3$H$_2$], one of four structurally related phosphonic acid derivatives, isolated from *Streptomyces*, is currently the most interesting natural phosphonate antibiotic [7].

The synthesis and structural studies of oxaphosphinine derivatives have been one of the main research focus points of our laboratory in the last decade. The X-ray and spectroscopy analysis, as well as biological activity studies have been carried out for this group of compounds [8–16]. The X-ray studies on the interactions in the crystal lattice have showed that the intramolecular hydrogen bond, producing a graph set motif of S6 [17, 18], is a common feature of the studied oxaphosphinine derivatives. The presence of the intramolecular N–H···O H-bond has been also confirmed by the ^{1}HNMR spectrum where the signal of N–H proton appeared with the chemical shift of 14 ppm.

This type of hydrogen bond is called the resonance-assisted hydrogen bond (RAHB) and has been a subject of extensive experimental and computational studies [19–31]. Gilli et al. [19–31] defined RAHB as the hydrogen bond where donor and acceptor are connected by a π-conjugated

EL: the new aromaticity measure based on one-electron density function

Justyna Dominikowska · Marcin Palusiak

Abstract Ellipticity of the bond, being the quantity which numerically reflects how far the given chemical bond has elliptic cross-section, may be used to estimate π-electron contribution in bonding. We make use of that fact and develop a new measure of aromaticity—EL index. Since ellipticity is available from calculations on one-electron density function, EL can be used for both theoretical and experimental data. The EL measure is normalized to make interpretation of this parameter as easy and comfortable as possible. We compare EL values with the values of other commonly used aromaticity measures, such as HOMA, PDI, FLU, and NICS. It appears that the indications of EL are in agreement with indications of other indices and general expectations.

Introduction

Although it is one of the most important concepts in chemistry, aromaticity still has no unified definition [1–3]. It was postulated in many reports [4–14] and summarized in Tetrahedron report 520 [3] that aromaticity is a collective phenomenon and hence a variety of criteria should be used in the discussion of this term in any particular subject of investigation [15]. For this

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reason several measures of aromaticity were introduced on the basis of unique physical and chemical properties of the species considered to be aromatic. In general, aromaticity is directly associated with the specific π-electronic structure resulting from the delocalization of π-electrons along the sequence of bonds forming the aromatic ring. This particular property of aromatic systems is responsible for unique geometrical, magnetic, and electron properties which in turn are reflected in chemical behavior of aromatic species. There are different aromaticity indices which were thoroughly used to estimate the aromatic character. Let us mention here the most successful ones such as HOMA [16, 17]—based on molecular geometry, NICS [18, 19]—based on induced magnetic ring currents, and finally those based on the properties of electron density function, e.g., PDI (π-electron delocalization index) [20], FLU (*fluctuation* index) [15] or MCI (multi-center index) [21, 22], BOIA (bond order index of aromaticity) [22], and θ index [23]. It is remarkable that all aromaticity measures defined on the basis of properties of electron density function are based on the number of electrons shared by two or more atomic centres (or atomic basins in accordance with the quantum theory of atoms in molecules (QTAIM) [24]). In other words, those aromaticity measures are constructed on di- or multi-center indices. Because of this the one-electron density function (e.g., this obtained in experimental charge density measurements) is not a sufficient source of information for the estimation of the above-mentioned electron density-based aromaticity indices.

In this article, we introduce a new measure of aromaticity based on hessian eigenvalues obtained from one-electron density function[1]. This new and easy to use index

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[1] We define the term one-electron density as the probability of finding the single electron in the given point of space, no matter which one of the electrons of the molecular system it is.

ORIGINAL RESEARCH

Co-crystal/salt crystal structure disorder of trichloroacetic acid–N-methylurea complex with double system of homo- and heteronuclear O–H···O/N–H···O hydrogen bonds: X-ray investigation, ab initio and DFT studies

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Abstract The X-ray diffraction studies revealed disorder of a trichloroacetic acid–N-methylurea complex crystal structure, connected with a proton transfer via O–H···O hydrogen bond. The observed structure corresponds to a co-existence of ionic (salt) and neutral (co-crystal) forms of the complex in the solid state in ratio 3:1, respectively. The geometrical analysis based on ab initio and density functional theory methods combined with the experimental research indicated that two different N-methylurea molecular conformations, defined by CNCN torsion angle, correspond to the neutral and the ionic form of the complex, respectively. The conformational changes seem to be connected with stabilization of the ionic structure after a proton transfer, as according to theoretical calculations this form of the complex (the ionic one) was unstable in the gas phase. A particular attention was focused on a system of a double intermolecular hydrogen bonds, O–H···O and N–H···O which join molecules into the title complex. The analysis of these interactions performed in terms of their geometry, energetic and topological electron density properties let for their classification into strong and medium strength hydrogen bonds. It was also found that the antibonding hydrogen bonding donor orbital occupation corresponded to the stabilization energy resulting from charge transfer in hydrogen bonds. Hence, it is postulated as a possible indicator of interaction strength.

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Introduction

Non-covalent interactions have received much interest due to their importance in stabilizing of the molecular arrangement crystal structure in the solid state [1–3]. They range from strong ones, as conventional hydrogen bonds, to weaker as for example van der Waals interactions. Among them the hydrogen bonds are the most favorite and useful in view of their high energy and directionality [4, 5].

Many researches are devoted to very strong hydrogen bonds, because of their important role as a transition state in biochemical reactions and enzyme catalysis [6–12]. Their unusual stabilization energy makes them to be distinguished from ordinary hydrogen bonds. All cases of strong and very strong hydrogen bonds have been classified into charge assisted hydrogen bond (CAHB) and resonance assisted hydrogen bond (RAHB) [13] which have been widely studied [14–23]. The enhancement of hydrogen bonding energy by additional factors, as the polarity of the donor and acceptor groups, can lead to proton transfer between molecules with formation of a salt. In order to convert a neutral hydrogen bond D–H···A into a corresponding ionic one $D^-···H–A^+$, external electric field may be required [24–27]. It can be produced by solvent dipoles or the assembly of many hydrogen bond bridges of the same type for example in crystal structure. Proton transfer enables charge and energy transfer in solid chemical and biological systems, thus a degree of cooperativity between these processes occurs.

The further insight into the nature of many types of hydrogen bonds, can be achieved by designing and studying

Synthesis, single-crystal and solution structure analysis and *in vitro* cytotoxic activity of two novel complexes of ruthenium(II) with *in situ* formed flavanone-based ligands.†

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Synthesis, structure and properties of two new flavanone complexes of Ru(II) are described. The new complexes form during the reaction of ruthenium(III) chloride with 3-aminoflavone (3-af) dissolved in an aliphatic alcohol. The formed products depend on the alcohol used and were found to be: *cis*-dichloridobis(3-imino-2-methoxyflavanone)ruthenium(II)·3H$_2$O (**1**) from a methanolic solution and *cis*-dichloridobis(3-imino-2-ethoxyflavanone)ruthenium(II)·2H$_2$O (**2**) from an ethanolic solution, in which the original ligand 3-af had been converted by dehydrogenative alcoholysis to an entirely new ligand. This paper presents the X-ray structure and detailed ¹H-NMR analysis of both new compounds, as well as the study of their antiproliferative activity. The coordination of Ru(II) is octahedral with [RuCl$_2$N$_2$O$_2$] chromophores, having *trans* chlorides and common Ru–L distances. Both **1** and **2** are highly cytotoxic towards the cisplatin resistant EJ and L1210 cell lines, and both complexes are as active as cisplatin in the sensitive cell lines. They display the ability to overcome cisplatin resistance in the drug resistant sub-lines EJcisR and L1210R. The present evidence suggests that the mechanism of biological activity may be different for these ruthenium compounds compared to cisplatin.

Introduction

Complexes of ruthenium(III) and ruthenium(II) have been found in recent years as interesting groups of compounds with potential anticancer activity. In many *in vitro* and *in vivo* studies they showed cytotoxic, pro-apoptotic and antimetastatic properties[1–3] often also able to overcome cisplatin-resistance.[4] Up till now only two compounds, namely NAMI-A, (*trans*-imidazolium[tetrachlorido(dimethylsulfoxide)imidazole-ruthenate(III)]) and KP 1019 (*trans*-indazolium[tetrachloridobis-(indazole)ruthenate(III)]) are currently being clinically tested.[5,6]

Ruthenium compounds often produce low systemic toxicity and good selectivity towards cancer cells.[7] Some evidence suggests that their affinity to transferrin enhances the selectivity, as cancer cells usually have more transferrin receptors (higher iron need) than normal cells.[8] Ru(II) complexes are more cytotoxic than those of Ru(III), and the latter may be reduced in tumour cells—

the hypothesis is known as "activation by reduction" (solid tumours create a hypoxic and a more acidic environment than the surrounding tissues, due to a poorer blood supply and higher metabolism).[9]

Depending on the ligands used in syntheses, the compounds may also act as topoisomerase poisons, or as other enzyme inhibitors.[10] The ruthenium central ions may coordinate DNA molecules (like guanine base), increase free radicals concentration and act even as photoactive agents.[10–13]

A suitable new ligand appeared to be 3-aminoflavone (3-af),[14] as it has the possibility to chelate *via* N and O to transition metal ions. The crystal structures of free 3-aminoflavone (3-af) and its coordination compound of formula [Cu(3-af)$_2$(NO$_3$)$_2$] were recently determined.[15,16] In the latter compound the copper ion is octahedrally surrounded by two amino nitrogen atoms and two carbonyl oxygen atoms. Two chelating 3-af ligands form the short bonds, and two coordinated nitrate ions occupy the axial positions.

It appeared interesting to check if this ligand would chelate to ruthenium in a similar way and to see whether the formed compound would display anticancer activity.

The present paper deals with the synthesis, properties and biological activity of ruthenium(II) compounds formed from 3-aminoflavone (3-af) and Ru(III) ruthenium(III) chloride. Most surprisingly, and depending on the used alcoholic solvent (MeOH, EtOH), the flavone ligand was oxidized, while solvolysing to form a 3-imino-2-alkoxyflavanone as a chelating ligand to ruthenium (see Scheme 1 below); meanwhile the ruthenium had been reduced to divalent ruthenium. The synthesis, spectral properties, 3D structure and antiproliferative (*in vitro*) activity of the 2 new compounds are described below.

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