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Electrostatic potential at nuclei as a reactivity index in hydrogen bond formation. Complexes of ammonia with C–H, N–H and O–H proton donor molecules

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Abstract

In this study the use of molecular electrostatic potential at atomic sites as a reactivity descriptor for the process of hydrogen bonding is evaluated for a series of complexes involving different types of proton donor molecules and ammonia as a model proton acceptor. The compounds studied were: C_2H_4, $CH_3C{\equiv}CH$, $CH_2{=}CH{-}C{\equiv}CH$, HCN, CH_3NH_2, $(CH_3)_2NH$, HNC, $C_6H_5NH_2$, cytosine, HCONHCH3, CH_3OH, C_2H_5OH, C_3H_7OH, C_6H_5OH, HCOOH and H_3CCOOH. Geometry optimisation and vibrational frequency calculations at the optimised geometry were performed for isolated monomers and hydrogen-bonded systems. Density functional theory computations at the B3LYP/6-31G(d,p) were employed. Linear dependence between the molecular electrostatic potential at the hydrogen atom in the isolated monomers and the energy of hydrogen bond formation is found. The results show that the electrostatic potential at atomic sites can be used as a reactivity descriptor for the ability different types of proton donor molecules to form hydrogen bonds.

Keywords: Hydrogen bonding; Electrostatic potential; Reactivity index; Descriptor

1. Introduction

In previous studies from this laboratory [1–3], it was shown that the electrostatic potential at nuclei (EPN) can be applied as a highly accurate descriptor of the ability of molecules belonging to several different classes to form hydrogen bond complexes either as proton donors or proton acceptors. Excellent linear relationships between theoretically estimated electrostatic potential values at nuclei, V_Y, and binding energies were found [1–3]. These studies are summarized in a review [4]. The physical foundations of these dependences were theoretically substantiated [4] by applying the Morokuma energy decomposition analysis [5–7]. The above studies treated the application of EPN values as reactivity descriptors for the hydrogen bond formation within separate series of proton donors or proton acceptor molecules.

In view of the importance of hydrogen bonding for essential properties of physical, chemical and biological systems, it is of interest to define a descriptor

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that would quantify the reactivity of molecules having different types of proton donors or proton acceptor sites. The aim of the present study is to assess the potential applicability of the EPN as a reactivity descriptor for a series of molecules containing C–H, N–H and O–H bonds as proton donors. Ammonia is used as a model proton acceptor in the respective complexes.

The key role of electrostatic forces in hydrogen bonding has long been established [8–26]. Thus, theoretically estimated or experimental molecular quantities linked to the electric charge distribution in molecules are of interest in the search for appropriate reactivity descriptors for the hydrogen bonding process. Atomic charges at the proton donor and acceptor atoms as well as maxima and minima of the molecular electrostatic potential are natural choices in this respect. The positions of minima of the molecular electrostatic potential associated with electron donating centres in isolated monomer have been successfully used to predict the sites and directionality of hydrogen bonds in a number of systems [23–25]. In most of these studies, properties of the molecular surface electrostatic potential have been used. Descriptors for hydrogen bonding are also essential in QSAR studies [26,27].

In this work, hydrogen-bonded complexes of ammonia with 16 proton donor molecules with C–H, N–H and O–H bonds as proton donor sites are studied by density functional theory computations. The proton donor molecules are:

C–H proton donors: $H_2C{=}CH_2$, $H_3C{-}C{\equiv}C{-}H$, $H_2C{=}CH{-}C{\equiv}C{-}H$, HCN
N–H proton donors: CH_3NH_2, $(CH_3)_2NH$, $C^{-}{\equiv}N^{+}{-}H$, $C_6H_5NH_2$, cytosine, $HCONHCH_3$
O–H proton donors: CH_3OH, C_2H_5OH, C_3H_7OH, C_6H_5OH, HCOOH, CH_3COOH

Dependences between binding energy and a number of local structural, spectroscopic and electric charge parameters associated with the sites of the hydrogen bond formation were studied. The principal focus of interest was the applicability of local electric charge parameters, such as partial atomic charges and EPN, in quantifying the reactivity of monomer proton donor molecules for the process of hydrogen bonding.

2. Computational details

Density functional theory computations at B3LYP/6-31G(d,p) [28–30] level were carried out to evaluate properties of isolated molecules and hydrogen-bonded complexes. The obtained interaction energies were also corrected for zero-point vibrational energies, basis set superposition error (BSSE) [31] and fragment relaxation energy contributions [32]. A scaling factor for B3LYP/6-31G(d,p) vibrational frequencies $k = 0.9804$ was used [33]. All calculations were carried out with the GAUSSIAN 98 program package [34].

Electric charge properties of the isolated compounds were theoretically determined in order to describe the reactivity of the molecules studied with respect to the process of hydrogen bonding with ammonia. Atomic partial charges, calculated according to the schemes of the Mulliken [35], Breneman and Wiberg (CHELPG) [36], Kollman and coworkers (MK) [37] and Bader ('Atoms-in-Molecules', AIM) [38] were estimated using the GAUSSIAN 98 set of programs.

The molecular electrostatic potential values at the site of the hydrogen atoms were also evaluated. The electrostatic potential at a particular nucleus (A) is defined by Eq. (1) at $r = R_Y$ (radius vector of the hydrogen nuclei) as the term at $R_Y = R_A$ is dropped out [39,40]:

$$V_Y{\equiv}V(R_Y) = \sum_{A\neq Y} \frac{Z_A}{|R_Y - R_A|} - \int \frac{\rho(r')}{|R_Y - r'|}\mathrm{d}r' \quad (1)$$

In this equation, Z_A is the charge on nucleus A with radius vector R_A, $\rho(r)$ is the electronic density function of the respective molecule and r' is a dummy integration variable. Eq. (1) is written in atomic units and contains a summation over all atomic nuclei, treated as positive point charges as well as integration over the continuous distribution of the electronic charge. The molecular electrostatic potential values at each atom of the isolated monomer are obtained using the GAUSSIAN 98 set of programs [34].

3. Results and Discussion

The determination of the relative reactivity of different sites in a molecule with respect to hydrogen

bonding is a key issue in QSAR studies. As is well known, hydrogen bonding is considered one of the principal mechanisms for drug-receptor interactions [41–43]. A number of different types of reactivity descriptors of hydrogen bonding have been proposed and tested [42–47]. In this paper, we explore the potential of several local molecular parameters, characterising the electric charge distribution in molecules, as reactivity descriptors for the process of hydrogen bonding. Complexes involving molecules with C–H, N–H and O–H bonds as proton donor sites were studied. Ammonia is used as a model proton acceptor. Partial atomic charges calculated according to the methods of Mulliken [35], CHELPG [36], MK [37], and AIM [38] were evaluated. The electrostatic potential at the hydrogen atoms of the proton donors were also theoretically determined. The hydrogen-bonded complexes were further characterised by the usual dependences between binding energies and changes in bond lengths and vibrational frequencies. The theoretically estimated energies of hydrogen bond formation corrected for zero-point vibrational energy (ΔE^{zpe}), BSSE (ΔE^{bsse}) and fragment relaxation energy (ΔE^{rel}) contributions for all complexes studied are presented in Table 1. The fully corrected energies are given in the ultimate column of the table. The optimised structures of the hydrogen-bonded complexes for some molecules of the series are shown in Fig. 1.

3.1. Dependence between binding energies and shifts of bond lengths and vibrational frequencies

Selected structural parameters of the complexes studied are presented in Table 2. These are the changes in the X–H lengths with respect to bond length in the isolated molecules (Δr_{X-H}) and the hydrogen bond length $r_{H\cdots N}$. As can be expected, the X–H bond length increases with hydrogen bond formation. The dependence between changes in X–H bond lengths and binding energy is shown in Fig. 2. The linear regression correlation coefficient is calculated to be 0.923. The vibrational frequency shifts upon complexation for the X–H (X = C, N, O) bond-stretching mode ($\Delta\nu_{X-H}$) are also given in Table 2. The X–H stretching frequency decreases with the formation of the hydrogen-bonded complexes, due to the weakened X–H bonds in the dimers. The relationship between the energy of hydrogen bond formation and the change in X–H stretching

Table 1
B3LYP/6-31G(d,p) ab initio calculated non-corrected energy of hydrogen bond formation (ΔE), zero-point vibrational energy correction (ΔE^{zpe}), BSSE (ΔE^{bsse}), relaxation correction (ΔE^{rel}) and totally corrected energy (ΔE^{cor}) for complexes of ammonia and molecules containing C–H, N–H and O–H proton donor sites

Molecule	ΔE	ΔE^{zpe}	ΔE^{bsse}	ΔE^{rel}	ΔE^{cor}
$H_2C{=}CH_2$	−1.9747	0.7918	0.7888	0.0429	−0.3512
$H_3C{-}C{\equiv}C{-}H$	−4.3542	1.2427	0.8384	0.1105	−2.1626
$H_2C{=}CH{-}C{\equiv}C{-}H$	−5.0033	1.3006	0.8463	0.1250	−2.7314
HCN	−9.2762	1.8666	0.8501	0.3079	−6.2516
CH_3NH_2	−4.2284	1.1861	1.0416	0.0894	−1.9113
$(CH_3)_2NH$	−4.5042	1.0717	1.0889	0.0552	−2.2884
$C^{-}{\equiv}N^{+}{-}H$	−13.9419	2.9992	0.3430	0.9629	−9.6368
$C_6H_5NH_2$	−6.6399	1.4033	1.0890	0.2056	−3.9420
Cytosine[a]	−8.7649	1.5430	1.0106	0.3762	−5.8351
$HCONHCH_3$	−8.2512	1.5153	0.8892	0.2663	−5.5804
CH_3OH	−8.8950	1.8063	1.1198	0.2766	−5.6923
C_2H_5OH	−8.8022	1.7201	1.1384	0.2788	−5.6649
C_3H_7OH	−8.8431	1.6820	1.1175	0.3095	−5.7341
C_6H_5OH	−11.4756	1.8850	1.1224	0.5747	−7.8935
HCOOH	−15.4194	2.2997	1.2422	1.5949	−10.2826
CH_3COOH	−14.6239	2.1772	0.5812	1.8469	−10.0186

All values are in kcal/mol.
[a] The N–H proton donor bond in cytosine is specified in Fig. 1.

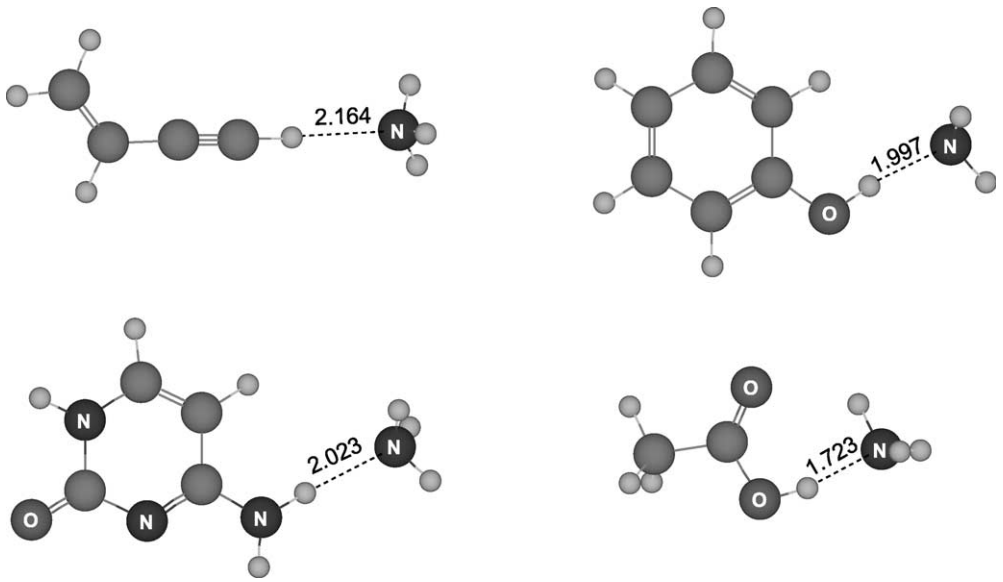

Fig. 1. Optimised structures of hydrogen-bonded complexes of vinyl acetylene, phenol, cytosine and acetic acid with ammonia form B3LYP/6-31G(d,p) computations.

frequency $\Delta\nu_{X-H}$ in the series of molecules studied is shown in Fig. 3.

The correlation coefficients obtained for the above two dependences are not particularly high. Compared to the analogous relationships for complexes of molecules belonging to a particular class of compounds [1–4], the respective correlation coefficients for the present series are distinctly

Table 2
B3LYP/6-31G(d,p) ab initio calculated values of hydrogen bond length $r_{H\cdots N}$ (in Å), changes in the monomeric X–H bond length Δr_{X-H} (in Å), X–H stretching mode frequencies and shifts (in cm^{-1}) for the molecules studied and their hydrogen-bonded complexes with ammonia

Molecule	r_{X-H}[a]	r_{X-H}^{compl}[b]	Δr_{X-H}[c]	ν_{X-H}[a]	ν_{X-H}^{compl}[b]	$\Delta\nu_{X-H}$[c]	$r_{H\cdots N}$
$H_2C{=}CH_2$	1.0867	1.0890	0.0023	3247	3232	−15	2.5478
$H_3C{-}C{\equiv}C{-}H$	1.0651	1.0789	0.0138	3492	3299	−193	2.1850
$H_2C{=}CH{-}C{\equiv}C{-}H$	1.0652	1.0802	0.0150	3491	3279	−212	2.1637
HCN	1.0691	1.0948	0.0257	3476	3116	−360	1.8218
CH_3NH_2	1.0172	1.0233	0.0061	3533[d]	3422	−111	2.2100
$(CH_3)_2NH$	1.0165	1.0277	0.0112	3521	3431	−90	2.1811
$C^{-}{\equiv}N^{+}{-}H$	0.9987	1.0402	0.0415	3833	3112	−721	1.7755
$C_6H_5NH_2$	1.0110	1.0224	0.0114	3621[d]	3405	−216	2.0730
Cytosine	1.0065	1.0214	0.0149	3676[d]	3398	−278	2.0229
$HCONHCH_3$	1.0091	1.0244	0.0153	3643	3380	−263	2.0154
CH_3OH	0.9652	0.9809	0.0157	3825	3478	−347	1.9125
C_2H_5OH	0.9655	0.9812	0.0157	3823	3525	−298	1.9135
C_3H_7OH	0.9654	0.9812	0.0158	3824	3522	−302	1.9098
C_6H_5OH	0.9661	0.9899	0.0238	3823	3351	−472	1.9967
HCOOH	0.9739	1.0161	0.0422	3733	3037	−696	1.7043
CH_3COOH	0.9722	1.0109	0.0387	3754	3009	−745	1.7230

[a] For isolated molecules.
[b] For hydrogen-bonded complexes.
[c] $\Delta r_{X-H} = r_{X-H}^{compl} - r_{X-H}$; $\Delta\nu_{X-H} = \nu_{X-H}^{compl} - \nu_{X-H}$.
[d] The averaged values between the N–H symmetric and antisymmetric stretching frequencies.

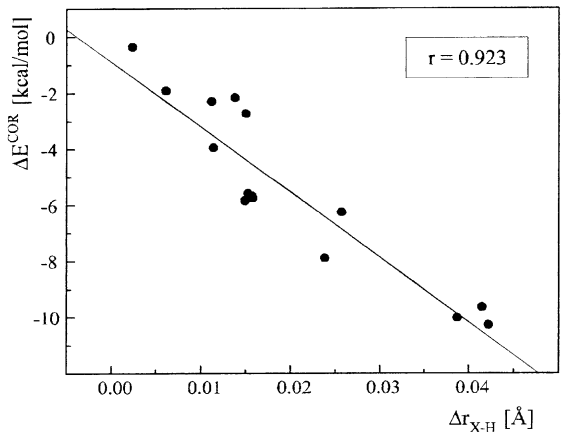

Fig. 2. Dependence between binding energy (ΔE^{cor}) and changes in X–H bond length (Δr_{X-H}) for the hydrogen bonded to ammonia complexes of molecules containing C–H, N–H and O–H proton donor sites.

lower. The finding is expected since the changes in structural parameters and vibrational frequencies are affected by factors that do not repeat within the series studied, such as atomic radii and masses of atoms. Nevertheless, it is interesting that these classical dependencies are retained within a series of complexes involving different types of proton donors.

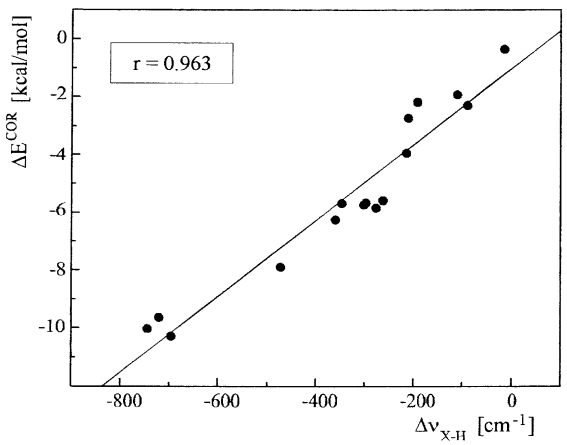

Fig. 3. Dependence between energy of hydrogen bond formation (ΔE^{cor}) and changes in X–H stretching frequency shifts ($\Delta \nu_{X-H}$) for the hydrogen bonded to ammonia complexes of the molecules studied.

3.2. Dependences between binding energy and partial atomic charges

As already underlined, the electrostatic interactions have a key role in hydrogen bond formation. It is expected that the partial atomic charges would characterise the reactivity of the respective sites in the molecules toward the complexation process. It was of interest, therefore, to assess the applicability of several types of theoretical partial atomic charges as reactivity descriptors for hydrogen bonding. It should be noted that the descriptors refer to properties of the monomer molecules. Mulliken partial charges, the electrostatic potential derived CHELPG and MK charges, and AIM charges were determined. The results are presented in Table 3.

The four types of partial atomic charges at the binding site of the isolated molecules were plotted against the calculated binding energies. The results obtained can be summarized as follows:

(1) The Mulliken charges do not correlate well with the energy of hydrogen bond formation. The linear regression coefficient for the relationship if $r = 0.812$.
(2) The electrostatic potential-related charges CHELPG and MK also do not provide a satisfactory description of the ability of molecules studied towards the process of hydrogen bonding. The respective linear regression coefficients are $r = 0.498$ for CHELPG charges and $r = 0.478$ for MK charges.
(3) The charges obtained by AIM method also are not well correlated with the binding energies. The respective linear regression coefficient is $r = 0.779$.

In a previous study on complexes of monosubstituted acetylene derivatives with ammonia, it was shown that among these four types of partial atomic charges, the Bader's AIM charges [38] provide a satisfactory characterization of the binding ability of the respective acetylene derivatives. In the present series of molecules with different types of proton donor sites, however, none of the tested partial charges provided satisfactory description of the binding ability of the molecules studied.

Table 3
B3LYP/6-31G(d,p) ab initio calculated values of atomic charges (in units of electron) at the hydrogen atom in monomer molecules, Q_H, derived via different procedures (Mulliken, CHELPG, MK and AIM) and electrostatic potential V_H (in atomic units)

Molecule	$Q_H^{Mulliken}$ [a]	Q_H^{CHELPG} [b]	Q_H^{MK} [c]	Q_H^{AIM} [d]	V_H [e]
$H_2C{=}CH_2$	0.1012	0.1236	0.1449	0.0004	−1.1168
$H_3C{-}C{\equiv}C{-}H$	0.1477	0.2706	0.3154	0.1139	−1.0595
$H_2C{=}CH{-}C{\equiv}C{-}H$	0.1603	0.2683	0.2829	0.1247	−1.0493
HCN	0.2089	0.1886	0.2063	0.1849	−0.9826
CH_3NH_2	0.2361	0.3389	0.3438	0.3466	−1.0786
$(CH_3)_2NH$	0.2363	0.3428	0.3452	0.3352	−1.0789
$C^-{\equiv}N^+{-}H$	0.3014	0.2578	0.2726	0.5308	−0.9364
$C_6H_5NH_2$	0.2547	0.3367	0.3366	0.3837	−1.0421
Cytosine	0.2697	0.3831	0.3800	–	−1.0091
$HCONHCH_3$	0.2586	0.2807	0.2697	–	−1.0158
CH_3OH	0.3014	0.3876	0.3883	0.5698	−1.0149
C_2H_5OH	0.3040	0.3750	0.3743	0.5613	−1.0163
C_3H_7OH	0.3039	0.3982	0.4009	0.5619	−0.0161
C_6H_5OH	0.3160	0.4058	0.4098	0.5821	−0.9786
HCOOH	0.3238	0.4208	0.4248	0.6026	−0.9511
CH_3COOH	0.3220	0.4050	0.4011	0.6015	−0.9647

[a] Ref. [35].
[b] Ref. [36].
[c] Ref. [37].
[d] Ref. [38].
[e] V_H is the electrostatic potential at the side of the hydrogen atom in the X−H bond in isolated molecules.

3.3. Dependence between binding energies and EPN

Linear dependences with high correlation coefficients between binding energy and electrostatic potential at the sites of proton donor and proton acceptor atoms participating in hydrogen bonding were established for several classes of molecules [1–4]. It was, therefore, of interest to assess the applicability of this methodology for molecules belonging to different classes having proton donors of different nature. The calculated values for the electrostatic potential at the hydrogen atom, V_H, in molecules with C−H, N−H and O−H proton donors are given in the last column in Table 3. The plot between ΔE^{cor} and V_H is shown in Fig. 4. The respective linear regression equation is:

$$\Delta E^{cor} = -65.69 V_H - 59.16$$

$$n = 16,\ \ r = 0.973,\ \ \mathrm{sd} = 0.713$$

It is gratifying to find that a very good linear dependence between the two quantities is established. The result indicates that the EPN values are applicable in characterising the proton donor abilities of molecular sites having different environment of the hydrogen atom. It may be concluded that these quantities have wider application as reactivity descriptors for molecules with differing proton donor sites.

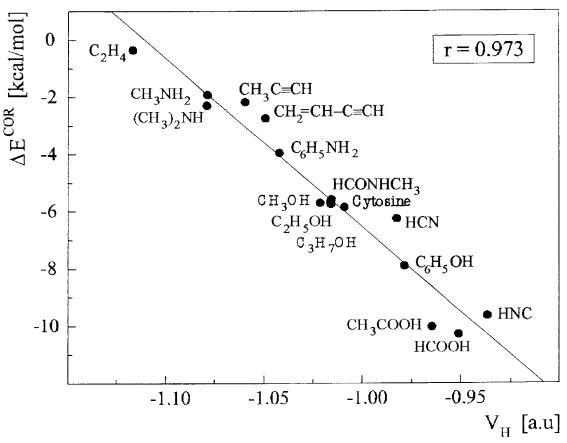

Fig. 4. Dependence between energy of hydrogen bond formation (ΔE^{cor}) and the electrostatic potential at the hydrogen atom in C−H, N−H and O−H binding sites of monomer molecules (V_H).

In a recent study, Bruns et al. [48] showed that the Koopman's energy for the core 1s electrons correlates perfectly with the EPN values for the same atomic centre evaluated earlier [1,2]. The authors thus revealed that, the Koopman's energy can also be used to characterise the hydrogen bonding ability of different sites in molecules.

Work is currently in progress to assess the applicability of EPN in describing the reactivity of different sites in biologically active molecules with respect to the binding process to protein receptor sites.

4. Conclusions

Density functional theory computations at the B3LYP/6-31G(d,p) level were used to characterise the binding affinity towards hydrogen bonding of 16 molecules containing C–H, N–H and O–H proton donors. Molecular parameters associated with the electronic density distribution in the molecules studied were tested as reactivity descriptors for the proton donor sites. The partial atomic charges evaluated form Mulliken population analysis, CHELPG, MK and AIM methods do not provide satisfactory description of the binding ability of the studied monomers for the complexation with ammonia. A very good linear dependence is found between binding energy and the electrostatic potential at the hydrogen atom of the proton donor sites. The results indicate that EPN values at the hydrogen atom can be used as descriptors representing quantitatively the reactivity of the proton donor monomers in the process of hydrogen bonding.

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