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Bifurcated Hydrogen Bonds: Three-Centered Interactions

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The nature of bifurcated or three-centered hydrogen bonds (HB) has been investigated. Different families of compounds were chosen: monomers with intramolecular three-centered HB, dimers with a HB donor (HBD) and a molecule with two HB acceptor (HBA) groups, and trimers with one HBD and two HBAs. All the systems were optimized at the B3LYP/6-31G* level, and, in the case of the complexes, the interaction energies were evaluated and corrected with the basis set superposition error (BSSE). The electronic nature of these three-centered HBs was analyzed by means of the atoms in molecules (AIM) approach. The present study indicates the existence of bifurcated bond paths in the AIM analysis with electron densities that can be classified as follows: (i) compounds with symmetric three-centered HBs presenting two symmetric bond critical points with equal values of electron density; (ii) compounds with asymmetric three-centered HBs presenting two bond critical points with different values of electron density; (iii) compounds with a regular HB and a van der Waals interaction showing two bond critical points with different electron density values one of which is very small; (iv) van der Waals complexes with two bond critical points having very small electron densities. Therefore, looking at the geometry, electron density, and energy results, the nature as HB of these three-centered interactions has been confirmed.

Introduction

As Jeffrey and Saenger explain in *Hydrogen Bonding in Biological Structures*[1] it was not until 1939 that chemists started to accept that there can be more than one simultaneous hydrogen bond (HB) acceptor group. It was then that Albrecht and Corey proposed a “bifurcated bond” (see configuration **1** in Figure 1) to explain the structural disposition of NH and C═O groups in the crystal structure of α-glycine,[2] which was confirmed later by X-ray and neutron diffraction studies.[3] Unfortunately, this term of “bifurcated HB” has been also used to define another configuration (see configuration **2** in Figure 1) that can correspond, for example, to certain water dimers and trimers.[4]

The objective of the present work is the study of the interactions described by the configuration **1** of Figure 1, and we will refer to them with the term three-centered HBs as defined by Jeffrey and Saenger[1]. These unusual HBs can be characterized as that configuration where an H atom is surrounded by three electronegative atoms, lying in or close to the plane delimited by them, and where this H atom is covalently bonded to one of the electronegative atoms and hydrogen-bonded to the other two. Different authors have been endowing the concept of three-centered HBs.[5] Thus, Donohue[6] showed different examples of crystal structures with three-centered bonds where two acceptor atoms were located at nearly the same distance from a hydrogen atom, both distances being shorter by around 0.3 Å than the sum of the van der Waals radii. In 1969, Parthasarathy[7] found that this kind of bond seemed to be very common in X-ray structures, and he suggested that the sum of the three angles formed by the H atom and the other three atoms should be near to 360°; in other words, the four atoms should be in or close to a plane.

These three-centered HBs have been used to explain a large number of biological structures and are commonly used by biochemists and biologists to account for certain interactions in biological systems. This is in agreement with the fact that three-centered HBs occur frequently in the crystal structures of zwitterionic amino acids (∼70%) as is shown by Jeffrey.[1] The analysis of neutron diffraction studies on pyranose, pyranoside sugars, amino acids, barbiturates, purines, pyrimidines, nucleosides, and nucleotides showed an excess of acceptors (HBA) over donors (HBD) and that a high percentage of the HBs are three-centered.[8]

Figure 1. Different configurations to which the term “bifurcated” has been applied. The term “three-centered interaction” only corresponds to configuration **1**.

These particular HBs have been investigated at a theoretical level to explain certain structures. Thus, by using molecular dynamics with AMBER it was found that three-centered HBs occur frequently in a DNA model.[9] Moreover, the role of these bonds in stabilizing nonplanar amino groups in DNA was studied by MO calculations at high levels of computation,[10] and a three-centered HB appears in the X-ray structure of the anti-AIDS compound 3′-azido-3′-deoxythymidine (AZT), which has been also studied at an ab initio level.[11]

Therefore, we are dealing with a quite “common” nonconventional HB whose nature has never been deeply investigated from a theoretical point of view. Continuing with our interest in the theoretical study of peculiar HBs,[12] we have chosen a number of systems where these three-centered HBs could be formed and we have studied their geometric and electronic data by means of the study of the topology of the electron density within the frame of the theory of atoms in molecules (AIM) established by Bader.[13] The systems studied have been clas-

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TABLE 1: HB Distances (Å) and Angles (deg), Electron Density at the Bond Critical Point (BCP), and the Corresponding Laplacian, Calculated at B3LYP/6-31G* Level, for the Structures of Family I, Intramolecular Three-Center HBs

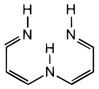
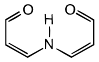
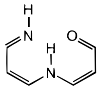
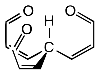
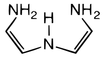
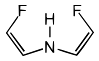
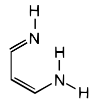
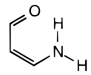
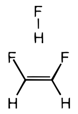
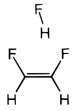
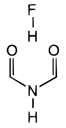
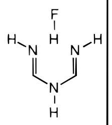
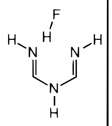
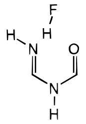
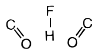
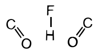
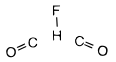
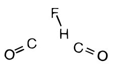
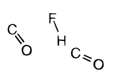
Structure	X···H distance	H–X distance	X–H···X angle	Symmetry	ρ_{bcp}	$\nabla^2\rho_{bcp}$
I1 	2.107 (*2)	1.033	123.80 (*2)	C_{2v}	0.0224 (*2)	0.0724 (*2)
I2 	2.050 (*2)	1.030	124.98 (*2)	C_{2v}	0.0232 (*2)	0.0766 (*2)
I3 	N...H 2.024 H...O 2.112	1.033	126.5 122.8	C_s	0.0267 0.0204	0.0839 0.0684
I4 	2.351 (*3)	1.088	124.2 (*3)	C_{3v}	0.0129 (*3)	0.0467 (*3)
I5 	2.471 (*2)	1.051	100.3 (*2)	C_{2v}	no HB found	
I6 	2.475 (*2)	1.011	97.9 (*2)	C_{2v}	no HB found	
I7 	1.950	1.023	130.27	C_s	0.0316	0.0965
I8 	1.929	1.020	124.98	C_s	0.0306	0.0986

TABLE 2: HB Distances (Å) and Angles (deg), Electronic Density at the Bond Critical Point (BCP), and the Laplacian, Calculated at B3LYP/6-31G* Level, for the Structures of Family II, Dimers Bonded by Three-Center HBs

Structure	X···H distance	H–F[a] distance	F–H···X angle	Symmetry	ρ_{bcp}	$\nabla^2\rho_{bcp}$
II1ts 	2.122 (*2)	0.936	140.4 (*2)	C_{2v}	0.0136 (*2)	0.0582 (*2)
II1m 	1.929 2.377	0.936	167.7 114.5	C_s	0.0216 0.0079	0.0767 0.0462
II2 	2.074 (*2)	0.940	136.5 (*2)	C_{2v}	0.0179 (*2) O···O 0.0124	0.0656 (*2) O···O 0.0443
II3ts 	2.068 (*2)	0.950	136.7 (*2)	C_{2v}	0.0221 (*2) N···N 0.0141	0.0725 (*2) N···N 0.0449
II3m 	1.941 2.216	0.952	143.6 130.1	C_s	0.0290 0.0163 N···N 0.0138	0.0897 0.0580 N···N 0.0440
II4 	H···N 1.833 H···O 2.423	0.951	149.5 126.7	C_s	0.0370 No HB N···O 0.0123	0.1103 No HB N···O 0.0411

[a] In the monomer, F−H = 0.934 Å.

TABLE 3: HB Distances (Å) and Angles (deg), Electronic Density at the Bond Critical Point (BCP), and the Laplacian, Calculated at B3LYP/6-31G* Level, for the Structures of Family III, Trimers Bonded by Three-Center HBs

Structure	X···H distance	H–F distance[a]	F–H···X angle	Symmetry	ρ_{bcp}	$\nabla^2\rho_{bcp}$
III1ts 	2.540 (*2)	0.935	104.8 (*2)	C_{2v}	No HB F···O 0.0085 (*2)	– F···O 0.0397 (*2)
III1m 	2.543 (*2)	0.935	104.4 (*2)	C_s	No HB F···O 0.0086 (*2)	– F···O 0.0401 (*2)
III2ts 	2.294 (*2)	0.939	115.8 (*2)	C_{2v}	0.0148 (*2)	0.0601 (*2)
III2m 	H...C 2.015 H...C 2.750	0.942	168.5 80.4	C_1	0.0258 No HB F···C 0.0123	0.0748 – F···C 0.0470
III3 	H...C 2.028 H...O 2.962	0.941	166.0 87.2	C_1	0.0252 No HB F···C 0.0100	0.0737 – F···C 0.0411
III4 F–H C=O	2.049	0.939	180.0	C_{∞}	0.0241	0.0708

[a] In the monomer, F−H = 0.934 Å.

sified by the number of molecules involved. Thus, we have the following three families.

I. Intramolecular three-centered HBs: both HBAs (F, N(H)═, and/or O═ groups) and the HBD (H−N or H−C groups) are parts of the same molecule. The set of molecules belonging to this family **I** are those represented in Table 1. Different three-centered intramolecular HBs have been described in the literature, including Katrusiak's X-ray structure for one of the tautomers of 1-phenyl-3-(2-hydroxyphenylamino)-2-buten-1-one,[14] where an NH group is simultaneously interacting with a C═O (forming a six-membered ring) and a C(OH)− (forming a five-membered ring) with a bifurcated HB. In another recent paper,[15] the copolymer of pyrrole and 2,1,3-benzothiadiazole is described by intramolecular bonding between the NH of the pyrrole unit and the N═ of the adjacent benzothiadiazole rings. These three-centered interactions are supported by ^{1}H NMR results and by the X-ray crystal of an oligomer consisting of two pyrrole rings bonded to a benzothiadiazole. More experimental evidence is given in a very recent study of three-centered intramolecular hydrogen bonding in oxamide derivatives by means of ^{1}H, ^{13}C, and ^{15}N NMR and X-ray diffraction studies.[16]

II. Dimers bonded by three-centered HBs: both HBAs are located in one molecule, whereas the HBD is an independent molecule. As HBD the HF molecule has always been used, and as HBAs F, O═, and N(H)═ groups have been chosen. The complexes studied are depicted in Table 2. Similar systems are found in the literature with the generic name of "superbases" or proton sponges. An example of these compounds could be 1,8-diaminonaphthalene derivatives, which are able to capture a proton very easily between both amino groups forming a stable H bridge between both N atoms.[17]

III. Trimers bonded by three-centered HBs: the trimers are formed by a molecule that is the HBD (HF) and two other

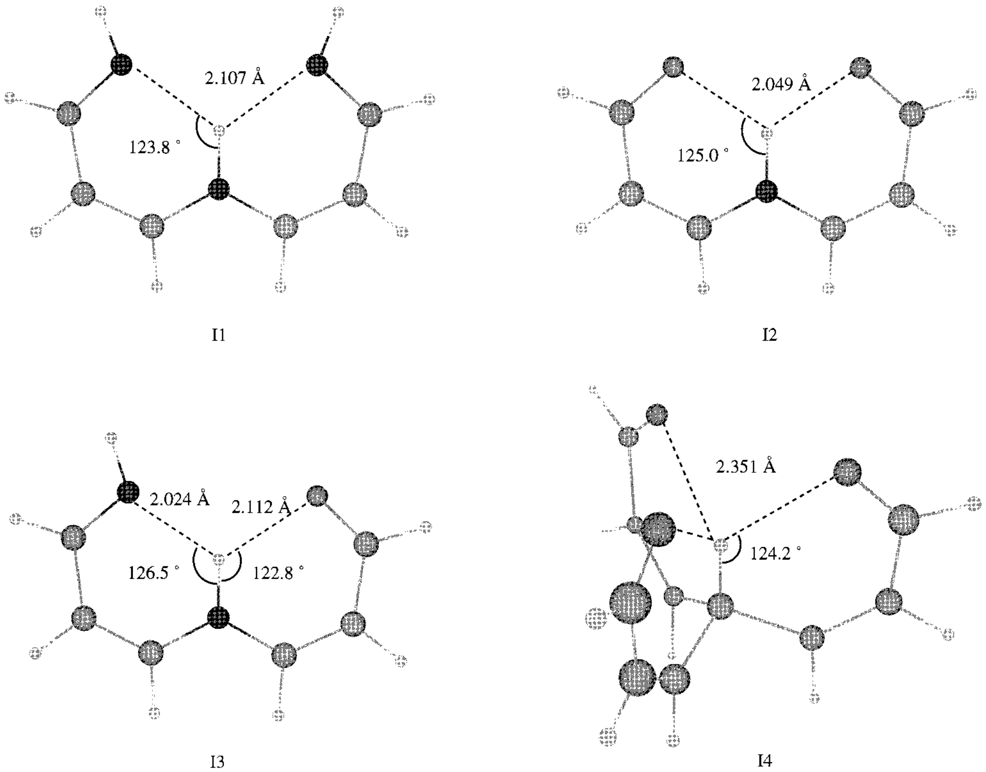


Figure 2. Structures of minimum energy found for the systems of family **I** where three-center interactions were present (**I1**−**I4**) calculated at the B3LYP/6-31G* level.

molecules that are HBAs (C═O). The possible complexes studied are represented in Table 3.

The question of three-centered interactions was studied also by Görbitz and Etter[18] who analyzed this kind of HB in a number of structures retrieved from the Cambridge Structural Database. These authors studied the existence of the three-centered HBs with carboxylate groups based mainly in geometric parameters. However, a detailed analysis of the electronic and energetic nature of these particular HBs, in a larger variety of systems, has not been embarked upon. Thus, the main goal of the current work is to present such an examination for a deeper understanding of these interactions so widely used by X-ray experts and biochemists to explain many structures.

Computational Methods

The calculations have been performed using the Gaussian 94 program.[19] All the molecular structures have been fully optimized with the 6-31G*[20] basis set using the hybrid density functional theory−Hartree−Fock method at the B3LYP[21] level. All the stationary points found were characterized as minima or transition structures by frequency calculations at the B3LYP/6-31G* level (all frequencies being positive in the first case or one and only one negative in the second case).

The zero-point vibrational energy (ZPE) has been calculated for all the complexes studied, and the interaction energies have been evaluated with and without this ZPE correction. Besides, these interaction energies (in the cases **II** and **III** where the systems are dimers and trimers) have been corrected for the inherent basis set superposition error (BSSE) by using the full counterpoise method[22] and the following equations:

$$\mathrm{BSSE(A{-}B)} = E(\mathrm{A})_{\mathrm{A}} - E(\mathrm{A})_{\mathrm{AB}} + E(\mathrm{B})_{\mathrm{B}} - E(\mathrm{B})_{\mathrm{AB}} \quad (1)$$

$$\mathrm{BSSE(A{-}B{-}C)} = E(\mathrm{A})_{\mathrm{A}} - E(\mathrm{A})_{\mathrm{ABC}} + E(\mathrm{B})_{\mathrm{B}} - E(\mathrm{B})_{\mathrm{ABC}} + E(\mathrm{C})_{\mathrm{C}} - E(\mathrm{C})_{\mathrm{ABC}} \quad (2)$$

where $E(\mathrm{A})_{\mathrm{AB}}$ or $E(\mathrm{A})_{\mathrm{ABC}}$ represents the energy of the monomer A calculated using its geometry within the dimer or the trimer and the complete set of basis functions used to describe the dimer or the trimer; $E(\mathrm{A})_{\mathrm{A}}$ is the energy of the same structure, but using only the basis functions centered on itself.

The electron densities, their Laplacians at the critical points of the HB interactions, and the H atomic charges (within the frame of the theory of atoms in molecules (AIM) proposed by Bader[13]) have been computed at the B3LYP/6-31G* level of calculation with the AIMPAC set of programs.[13b]

Results and Discussion

Geometry. The systems studied for each case (**I**−**III**) are shown in Tables 1−3, and the stationary structures found for each system are represented in Figures 2−4.

The interatomic distances and angles involved in the possible interactions for both the structures of minimum energy and the transition structures for the three families studied are gathered in Tables 1, 2, and 3, respectively.

In the set of compounds **I** (see Table 1), it is observed that the distances and angles between the proton of the central N−H or C−H group and the nearer two groups (N(H)═ or O═) are in agreement with the formation of a three-centered HB (four-centered HB in the case of **I4**), but only in cases where six-membered rings are formed (systems **I1**−**I4**). However, in those systems (**I5** and **I6**) where the creation of a three-centered HB would have implied the formation of five-membered rings, the distances between the central H atom and the HBAs are longer than those expected for a HB and the X−H···Y angles are smaller than 120.0°. Since all the systems where a three-centered HB is expected are planar, the Parthasarathy rule is followed. Symmetry was kept in all those systems where it was possible (**I1**, **I2**, and **I4**−**I6**). When compounds **I1**−**I3** are compared with compounds **I7** and **I8** (see Table 1), it is observed that the X(N,O)···H distances increase between 0.07 and 0.18

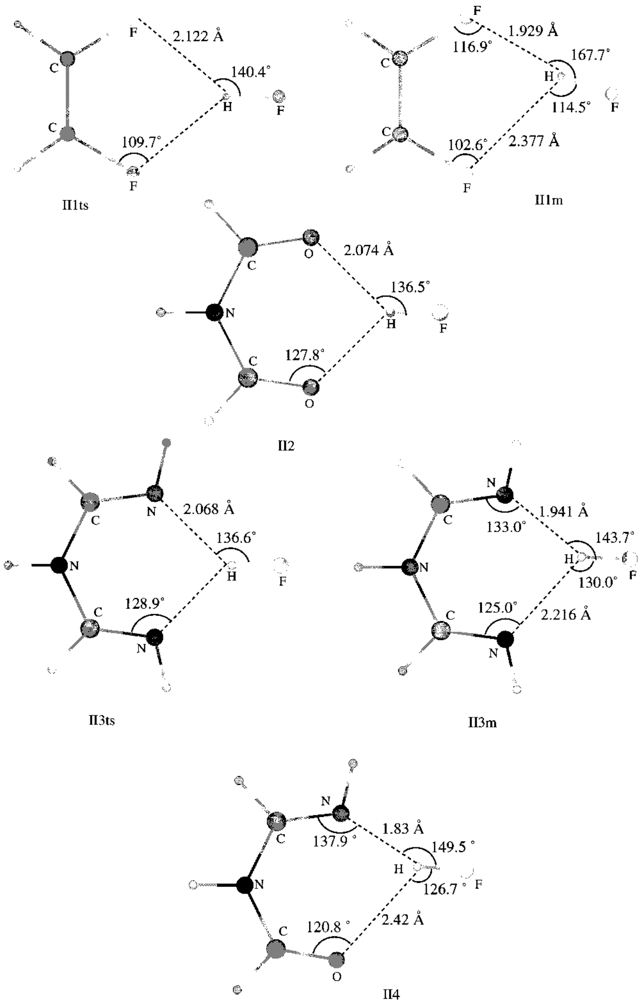


Figure 3. Structures of minimum energy and transition structures found for the systems of family **II** calculated at the B3LYP/6-31G* level.

Å when a three-centered bond can be formed. Nevertheless, the N−H distance of the donor group only increases by around 0.01 Å in the three-centered systems.

In the family of compounds **II** (see Table 2), the distances and angles obtained for the interaction with HF in all the dimers calculated (minima, m, and transition structures, ts) are in agreement with the formation of three-centered HBs in all the C_{2v} systems (**II1ts**, **II2**, and **II3ts**) and normal HBs with only one of the HBAs in the C_s systems (**II1m**, **II3m**, and **II4**). Nonetheless, if one closely examines the distances and angles of the latter compounds, the formation of asymmetric three-centered HBs leading to a six- (or five-) membered ring cannot be totally excluded. Table 2 highlights that the X···H distances are longer when a three-centered HB could be formed (**II1ts** and **II3ts**) than when only a two-centered HB is expected (**II1m** and **II3m**). Again, the planarity of all the systems fulfill the Parthasarathy rule.

From the distances and angles obtained for the trimers studied in set **III** (see Table 3) only the C_{2v} system where the H atom interacts with both C atoms (**III2ts**) can exhibit a three-centered HB [being Σ(angles around the H atom) = 351.9°]. The other two symmetric systems (**III1ts** and **III1m**) have interacting distances too long and angles too short. Compounds **III2m** and **III3** only could form normal HBs between the HF and one of the CO molecules.

Charge Density and AIM. For the discussion in this section we will follow some of the criteria for hydrogen bonding proposed by Koch and Popelier.[11]

(i) Charge Density (ρ_{BCP}) and the Laplacian of the Charge Density ($\nabla^2\rho_{BCP}$) at the Bond Critical Points (BCPs). Henceforth, van der Waals interactions (involving a H atom or not) will be referred as those with $\rho_{BCP} \approx 10^{-3}$ au and HBs as those with $\rho_{BCP} \approx 10^{-2}$ au. In all the systems, except for **I5** and **I6**, BCPs were found corresponding to van der Waals interactions, two-centered or three-centered HBs. The results obtained for the three sets studied are shown in Tables 1, 2, and 3, respectively. In systems **I1**−**I3**, **II1**(**ts**,**m**), **II2**, **II3**(**ts**,**m**), **III2**(**ts**,**m**), and **III3** there are three-centered interactions with two separated BCPs between the H atom of the HBD and two atoms of the HBAs. In the case of compound **I4**, a four-centered bond was found with three separated BCPs.

In the C_{2v} systems, the values of ρ_{BCP} obtained for both BCPs are $\sim 10^{-2}$ au, the quantities obtained for the $\nabla^2\rho_{BCP}$s are positive in all the cases, and these properties have the same value in the two BCPs of each system. The values obtained for these two parameters correspond to "closed-shell" interactions of the HB type, confirming the proposed HB nature for these three-centered interactions (see Table 1, systems **I1**, **I2**, and **I4**; Table 2, systems **II1ts**, **II2**, and **II3ts**; Table 3, system **III2ts**).

Those C_s systems where a three-centered HB was expected (**I3** and **II3m**) present asymmetrical three-centered interactions with two different BCPs each connecting the H and N(H)= or O= atoms of the HBA. The values of electron density and Laplacian are of the HB type (ρ_{BCP}s $\approx 10^{-2}$ au and positive $\nabla^2\rho_{BCP}$s). However, for the complex **II4** (which is very similar to **II3m**), only one regular HB between HF and the N(H)= group was found.

In the **II1m**, **III2m**, and **III3** systems, two different interactions (with two different BCPs) are found between the H atom and two atoms of the HBAs (two F atoms in **II1m**, two C atoms in **III2m**, and one C and one O atom in **III3**). However, by looking at the geometry and the value of the ρ_{BCP}s (see Tables 2 and 3), only one of the interactions could be considered as a HB, whereas the other one (that with the longest distance and the smallest ρ_{BCP} in each case) would be better classified as a van der Waals interaction.

In trimers **III1ts** and **III1m**, two symmetric BCPs are found between the HF and both CO molecules. But, because of their ρ_{BCP} and $\nabla^2\rho_{BCP}$ values and the fact that the BCPs are in the bond path of atoms other than H, these trimers are better described as van der Waals interaction complexes (see Table 3).

The creation of a HB would not be favored if it drives to the formation of a five-membered ring because the angular geometry is unfavorable with X−H···Y < 120° (≅108°)[1c]. This could explain why in compounds **I5** and **I6** no BCP was found between the central H atom and the possible HBAs (N or F).

In general, three-centered HBs cannot be considered as the sum of two independent regular HB, as it is noticed when comparing the ρ_{BCP}s found in compounds **I1**−**I3** and **III2ts** with those corresponding to the HB of compounds **I7**, **I8**, and **III4** (see Tables 1 and 3), which can be considered as the "half" of those molecules. In the four cases, a decrease of density is observed (**I1**, −0.0092; **I2**, −0.0074; **I3**, −0.0049 [O···H], −0.0102 [N···H]; **III2ts**, −0.0093). Thus, the sum of the two ρ_{BCP}s found in a three-centered HB is smaller than the sum of the ρ_{BCP}s found in the corresponding two-centered HBs ($\Sigma\rho_{BCP}$[**I1**] = 0.0448 < $\Sigma\rho_{BCP}$[2×**I7**] = 0.0632, $\Sigma\rho_{BCP}$[**I2**] = 0.0464

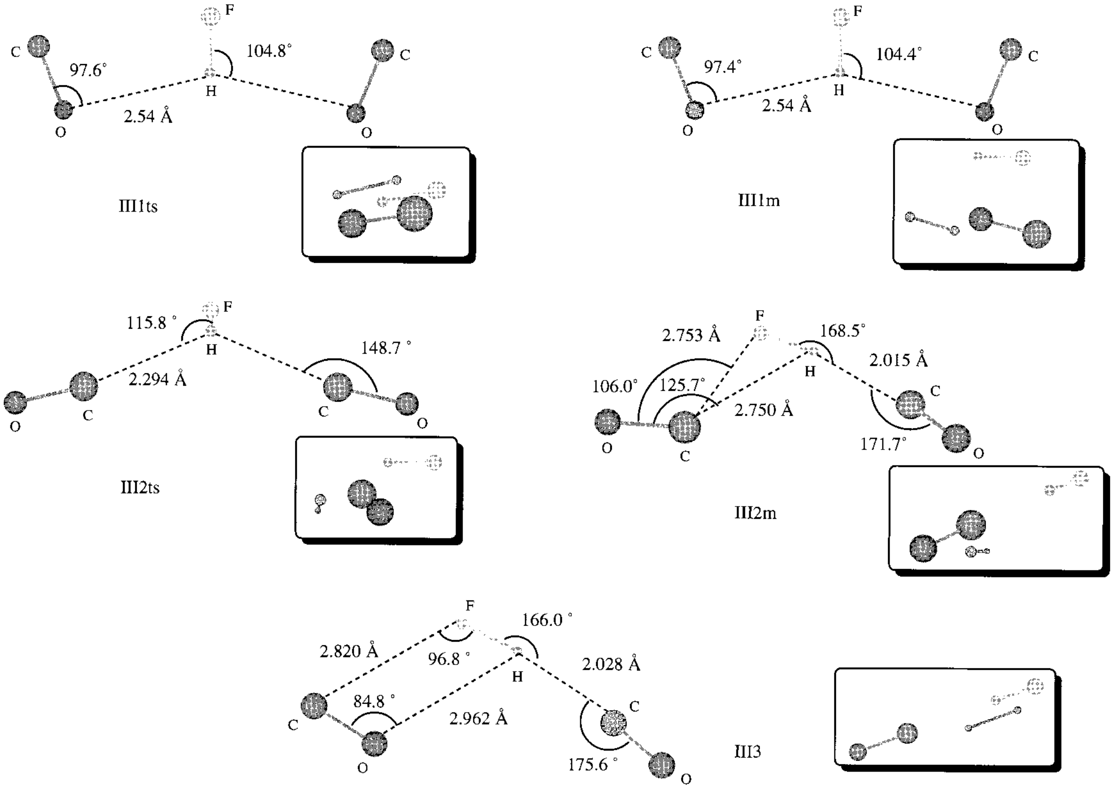


Figure 4. Structures of minimum energy and transition structures found for the systems of family **III** calculated at the B3LYP/6-31G* level.

$< \Sigma\rho_{\mathrm{BCP}}[2\times\mathbf{I8}] = 0.0612$, $\Sigma\rho_{\mathrm{BCP}}[\mathbf{I3}] = 0.0448 < \Sigma\rho_{\mathrm{BCP}}[\mathbf{I7},\mathbf{I8}] = 0.0622$, and $\Sigma\rho_{\mathrm{BCP}}[\mathbf{III2ts}] = 0.0296 < \Sigma\rho_{\mathrm{BCP}}[2\times\mathbf{III4}] = 0.0482$).

(ii) Topology. By analyzing the bond paths corresponding to these three families, we have found four different situations: systems with van der Waals interactions where, even though bond paths are found, they do not involve an H atom (**III1ts** and **III1m**); systems with only one two-centered HB and one bond path (**II4**); systems with one regular HB and a van der Waals interaction showing two different bond paths (**II1m**, **III2m**, and **III3**); systems with symmetric three-centered HBs with two different interaction lines, each one connecting the H atom (**I1**, **I2**, **I4**, **II1ts**, **II2**, **II3ts**, and **III2ts**); and systems with an asymmetric three-centered HB with two separated bond paths (**I3** and **II3m**). Some examples of the hydrogen-bonded systems and the corresponding interaction paths are represented in Figures 5−7.

(iii) Loss of Charge and Energetic Destabilization of the H Atom and Total Charge Transferred. Another criterion for the formation of a HB (regular or three-centered) is the loss of charge of the interacting H atom. This loss (ΔN) is computed by subtracting the electron population of the H in the free monomer from the corresponding H in the complex and should be negative (though some exceptions have been found, see refs 12e,g, with small positive ΔN, which could probably turn out to be negative within the integration error). This value only can be evaluated in systems with more than one molecule. The results obtained for sets **II** and **III** are shown in Table 4. In addition, this particular H atom should be destabilized in the complex, and this is measured by the difference in the total atomic energy between the H in the complex and in the monomer (see ΔE in Table 4), which should be positive. In all these complexes, the total charge transferred (ΔQ in Table 4) in the formation of the three-centered HB is always positive implying a donation of electrons from the HBA to the HF molecule.

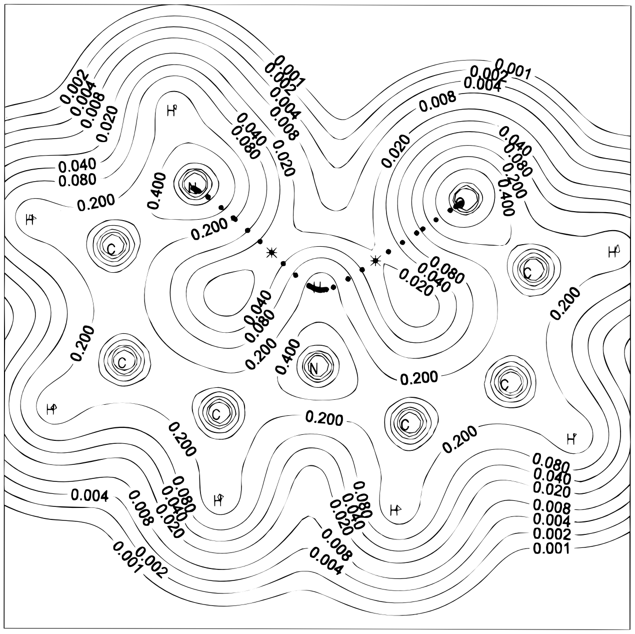


Figure 5. Contour plot of the electron density and bond paths of the symmetrical three-centered HB for compound **I3** calculated at the B3LYP/6-31G* level.

In a previous study,[12i] we found a direct relationship between the HB distance and the corresponding $\ln(\rho_{\mathrm{BCP}})$, which correlates both values in HBs and in covalent bonds. On the basis of that relationship and depending on the nature of the interacting atoms of each HB studied here, we have four different groups: H···F

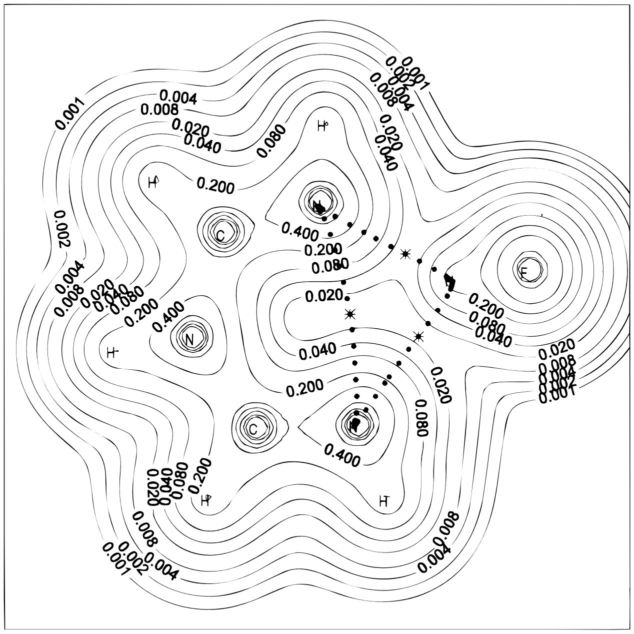


Figure 6. Contour plot of the electron density and bond paths of the asymmetrical three-centered HB of compound **II3m** calculated at the B3LYP/6-31G* level.

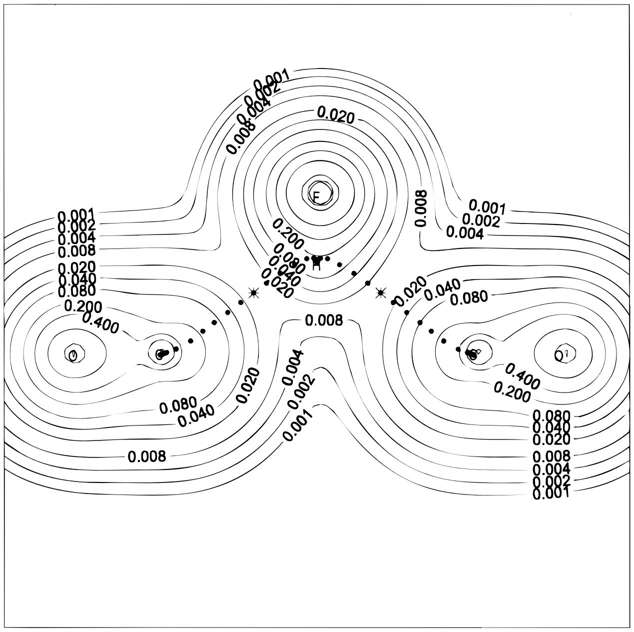


Figure 7. Contour plot of the electron density and bond paths of the symmetrical three-centered HB of compound **III2ts** calculated at the B3LYP/6-31G* level.

TABLE 4: Atomic Populations and Total Atomic Energies (au) of the Hydrogen Atom Involved in the HB and Total Charge Transferred (ΔQ, e) in the Formation of the Complexes, Calculated at B3LYP/6-31G* Level, for the Systems of Families II and III

structure	$N(H)_{cplx}$	ΔN^a	$E(H)_{cplx}$	ΔE^b	$N(F)_{cplx}$	ΔQ^c
II1ts	0.318	−0.013	−0.3005	−0.0055	9.693	0.011
II1m	0.317	−0.014	−0.3000	0.0060	9.696	0.013
II2	0.311	−0.020	−0.2922	0.0138	9.716	0.027
II3ts	0.304	−0.027	−0.2797	0.0263	9.746	0.050
II3m	0.306	−0.025	−0.2800	0.0398	9.746	0.052
II4	0.312	−0.019	−0.2859	0.0599	9.738	0.050
III1ts	0.321	−0.010	−0.2991	−0.0069	9.686	0.007
III1m	0.320	−0.011	−0.2990	0.0070	9.686	0.006
III2ts	0.320	−0.011	−0.2927	−0.0133	9.706	0.026
III2m	0.327	−0.004	−0.2949	0.0111	9.708	0.035
III3	0.330	−0.001	−0.2967	0.0093	9.707	0.037

[a] $N_{FH}(H) = 0.331$. [b] $E_{FH}(H) = -0.3060$. [c] $N_{FH}(F) = 9.6686$.

(**II1ts** and **II1m**), H···O (**I2**−**I4**, **I8**, and **II2**), H···N (**I1**, **I3**, **I7**, **II3ts**, **II3m**, and **II4**), and H···C (**III2ts**, **III2m**, **III3**, and **III4**). Within each of these groups, acceptable correlations were found between the HB distance and the corresponding $\ln(\rho_{BCP})$, and the equations found for each group are as follows:

$$\text{H}\cdots\text{F:}\quad d(\text{HB}) = 0.214 - 0.446\ln(\rho_{BCP}),\quad r^2 = 0.999,\quad n = 3,\quad \text{SD} = 0.011$$

$$\text{H}\cdots\text{O:}\quad d(\text{HB}) = 0.310 - 0.459\ln(\rho_{BCP}),\quad r^2 = 0.901,\quad n = 5,\quad \text{SD} = 0.056$$

$$\text{H}\cdots\text{N:}\quad d(\text{HB}) = 0.353 - 0.455\ln(\rho_{BCP}),\quad r^2 = 0.966,\quad n = 7,\quad \text{SD} = 0.025$$

$$\text{H}\cdots\text{C:}\quad d(\text{HB}) = 0.182 - 0.501\ln(\rho_{BCP}),\quad r^2 = 1.000,\quad n = 4,\quad \text{SD} = 0.001$$

Recently, we studied the additive properties of the ρ_{BCP}s in hydrogen-bonded complexes.[12h] We found a relationship between the "corrected" ρ_{BCP}s of the HBD ($\rho_{BCP}[01]$) and of the product of the hydrogen transfer ($\rho_{BCP}[02]$) and the ρ_{BCP}s at both sides of the H atom in the hydrogen-bonded complex ($\rho_{BCP}[1]$ and $\rho_{BCP}[2]$) expressed by eq 3, provided that the ρ_{BCP} of the monomers (HBD and HBA) are not exactly the values calculated for the isolated molecules but those "corrected" by the regression ρ_{BCP}(monomer in the complex) = $0.98\rho_{BCP}$(isolated monomer).

$$(\rho_{BCP}[01]/\rho_{BCP}[1]) + (\rho_{BCP}[02]/\rho_{BCP}[2]) = 1 \qquad (3)$$

This relationship is fulfilled in all the dimers and trimers with three-centered interactions here studied where the HBD is always HF ($\rho_{BCP}[01] = 0.3408 \times 0.98 = 0.3340$), the products of the hydrogen transfer were calculated at B3LYP/6-31G*, and the corresponding ρ_{BCP}s were evaluated for the H−R bond with the AIMPAC program and corrected by the 0.98 coefficient ($\rho_{BCP}[02] = 0.2670 \times 0.98 = 0.2617[C_2F_2H_3^+]$, $=0.2980 \times 0.98 = 0.2920[C_2H_4NO_2^+]$, $=0.3073 \times 0.98 = 0.3012[C_2H_6N_3^+]$, $=0.3152 \times 0.98 = 0.3089[C_2H_5N_2O^+]$, and $=0.2628 \times 0.98 = 0.2575[CHO^+]$). Consequently, by following eq 3, we found these results: 1.12 (**II1ts**), 1.12 (**II1m**), 1.11 (**II2**), 1.09 (**II3ts**), 1.09 (**II3m**), 1.07 (**II4**), and 1.11 (**III2ts**).

Energy. The evaluation of intramolecular interaction energies, or the possible stabilization gained with the formation of an intramolecular HB, is a controversial subject. Some authors[23] compare the energy of the intramolecular hydrogen-bonded system with that of the molecule in a different geometry where the HB is not possible. However, in that case the change in energy due to the change in conformation is not taken into account and, therefore, the final evaluation of the interaction energy does not reflect only that energy due to the HB interaction. Consequently, no discussion will be made from the energy results obtained for the monomers with intramolecular HBs belonging to family **I**. Their total energies are gathered in Table 5.

The energy results obtained for the dimers and trimers are also shown in Table 5. The ZPE and BSSE corrected interaction energies (E_{I+ZPE} + BSSE) calculated are, in general, in agreement with that expected for hydrogen-bonded complexes, except for the trimers **III1ts** and **III1m**. These two systems

TABLE 5: Total Energy, ZPE Correction, Interaction Energy, ZPE-Corrected Interaction Energy, BSSE Contribution, and Interaction Energy Corrected with ZPE and the BSSE for the Monomers (Family I), Dimers (Family II), and Trimers (Family III) Here Studied

structure	E_T (au)	ZPE (au)	E_I[a] (kcal/mol)	E_{I+ZPE}[a] (kcal/mol)	BSSE (kcal/mol)	E_{I+ZPE} + BSSE (kcal/mol)
I1	−398.254 138 3	0.148 973				
I2	−438.014 405 6	0.123 915				
I3	−418.135 470 4	0.136 469				
I4	−612.638 752 7	0.176 086				
I5	−322.036 690 7	0.137 212				
I6	−409.795 875 5	0.087 544				
II1ts	−377.470 247 5	0.047 619	−5.784	−4.932	3.11	−1.822
II1m	−377.470 307 5	0.048 156	−5.822	−4.633	3.11	−1.523
II2	−383.647 534 5	0.067 372	−9.726	−8.217	2.79	−5.427
II3ts	−343.881 668 9	0.092 566	−15.782	−14.092	3.20	−10.892
II3m	−343.881 675 5	0.092 833	−15.786	−13.928	3.17	−10.758
II4	−363.766 804 3	0.080 722	−13.362	−11.334	2.82	−8.514
III1ts	−327.045 699 9	0.021 118	−4.154	−2.907	4.62	1.713
III1m	−327.045 756 7	0.021 165	−4.189	−2.913	4.68	1.767
III2ts	−327.050 534 4	0.021 979	−7.187	−5.400	5.26	−0.140
III2m	−327.052 224 2	0.022 378	−8.248	−6.210	4.86	−1.350
III3	−327.050 968 1	0.022 030	−7.460	−5.640	4.51	−1.130

[a] Total energy (au) and ZPE-corrected energy (in parentheses) of the monomers: FH, −100.420 172 1 (−100.411 110); $C_2H_2F_2$, −277.040 858 173 (−277.003 658); $C_2H_3NO_2$, −283.211 862 218 (−283.155 958); $C_2H_4N_2O$, −263.325 338 783 (−263.256 911); $C_2H_5N_3$, −243.436 346 780 (−243.355 536); CO, −113.309 454 1 (−113.304 420).

have E_{I+ZPE}s around −3 kcal/mol. But the BSSEs calculated are so large that the final E_{I+ZPE} + BSSEs are positive and small. The BSSE effect is quite large for family **II**, as expected for a hybrid DFT−HF method with a medium basis set, and becomes even larger in the case of the trimers (set **III**).

Systems **II1m**, **III2m**, and **III3**, where only one regular HB was found (F−H⋯F and F−H⋯C), have E_{I+ZPE} + BSSEs of −1.52, −1.35, and −1.13 kcal/mol, respectively, which correspond to weak HBs and values already reported in the literature, such as −3.78 kcal/mol for the FH⋯FH system and −3.01 kcal/mol for the FH⋯CO system, both calculated at MP2/6-311++G** and BSSE corrected.[24]

The difference of E_{I+ZPE} + BSSE between the transition structure (with a three-centered HB) and the minimum (with a regular HB) of system **II1** is not extremely large (0.301 kcal/mol; see Table 5). Similarly, in the dimer **II3**, a symmetric three-centered HB is formed in the **II3ts** system and an asymmetric one is present in the **II3m** complex. Again, the difference in energy is small (0.134 kcal/mol).

The same situation is observed between the trimers **III2ts**, **III2m**, and **III3**. However, in this case, the difference in E_{I+ZPE} + BSSE between the first two systems is larger than that in the previous complexes (1.210 kcal/mol) as the two-centered HB is stronger than the three-centered one (see Table 5). Moreover, the difference in E_{I+ZPE} + BSSEs between **III2m** and **III3** (0.220 kcal/mol) indicates that when the HF molecule forms an extra van der Waals interaction, the strength of the HB diminishes but less than if a three-centered HB is formed.

A strong HB can exhibit E_Is between −12 and −24 kcal/mol.[25] Thus, compound **II4**, which forms only one HB (according with the electronic and geometry results), has a E_{I+ZPE} + BSSE value of −8.514 kcal/mol. This value is in agreement with that of a strong HB slightly disturbed by nearby interacting atoms (the O═ atom). In the case of compound **II2**, with an unambiguous three-centered HB, the E_{I+ZPE} + BSSE is clearly smaller (−5.43 kcal/mol) corresponding to a weak HB rather than to a strong one.

Therefore, it seems that a strong interaction such as a HB becomes weakened when another simultaneous interaction takes place, such as a weak van der Waals interaction or another HB as in the case of a three-centered HB.

In one of the first papers describing the theory of atoms in molecules, Carroll and Bader[26] already found a roughly linear relationship between ρ_{BCP} and the dissociation (interaction) energy. Following this idea, Mó et al.[4b] found a good linear correlation between the energies per HB and the corresponding electron densities at the BCP of a series of six water trimers when studying their cooperative effects at the HF/6-311++G(2d,2p) level of theory. In a previous paper,[12b] where eight systems with carbenes and silylenes as HBAs were analyzed, similar correlations between E_Is and ρ_{BCP}s (calculated at MP2/6-311++G** level) were found. Moreover, Koch and Popelier[11] found a good correlation between E_{IMPT} (interaction energy calculated by using the Hayes−Stone intermolecular perturbation theory on MP2/6-31G** optimized structures) and the sum of the ρ_{BCP} of all the intermolecular BCPs for the four systems studied (formaldehyde−chloroform, acetone−chloroform, benzene−formaldehyde, and 1,1-dichloroethane−acetone).

To reach a similar relationship, we have considered all the BCPs found in the area of interaction between the HBD (HF) and the HBAs in the hydrogen-bonded molecules of sets **II** and **III** and their corresponding E_Is (see Tables 2, 3, and 5). Thus, in all these systems, the values of ρ_{BCP}s for three-centered or two-centered HBs gathered in Tables 2 and 3 for each system were considered. However, along with the BCPs involved in the HB interactions some other BCPs were found for some of the complexes, and therefore, these were considered for the correlation. These systems were **II2**, **II3ts**, **II3m**, **II4**, **III2m**, and **III3**, and a BCP between the extremes of the HBAs (or between atoms other than H) was found (see Tables 2 and 3). By addition of all these ρ_{BCP}s and inclusion of those values of Mó et al.,[4b] our previous results with carbenes and silylenes,[12b] and those of Koch and Popelier,[11] a good correlation with E_I (E/HB for Mó et al., E_I for the carbenes and silylenes, and E_{IMPT} for Koch and Popelier cases) was obtained.

$$E_I = 1.174 \pm 0.757 - 268.681 \pm 26.067 \Sigma \rho_{BCP-int}, \quad r^2 = 0.947, \quad n = 27, \quad SD = 1.03 \quad (4)$$

In principle, if this correlation were universal, it would allow one to evaluate the E_I of monomers with intramolecular interactions (such as those belonging to set **I**) when all the ρ_{BCP}s involved in the interactions were known. Despite the fact that Mó et al.'s systems, our previous results, those of Koch and Popelier, and our present data are very diverse and the interaction energies provided by all of them and our present E_Is are calculated in a different way, the correlation found with the ρ_{BCP}s is quite good. This encouraged us to believe that this equation could be used in a predictive manner. Thus, by using the ρ_{BCP}s gathered in Table 1 for compounds **I1**−**I4** along with eq 4, an estimation of the possible E_Is for these compounds was done, finding the following values: −10.9 (**I1**), −11.3 (**I2**), −11.5 (**I3**), and −9.2 kcal/mol (**I4**), which are consistent with the rest of the E_Is obtained in this work.

Conclusions

Regarding the geometry, in sets **II** and **III**, the formation of regular HBs or three-centered HBs always elongates the HF bond. However, no relationship was found between the degree of deformation of the HBD (measured by the elongation of the HF bond from the monomer) and the kind of HB formed (regular, symmetric three-centered, or asymmetric three-centered).

Concluding, three-centered HBs are real HBs where the electron density is equally shared by an H atom and two HB-accepting atoms showing two different BCPs with similar characteristics of ρ and $\nabla^2\rho$. Energetically, they are weaker interactions than the regular HBs, and consequently, the HB distances become longer in three-centered HBs than in the regular ones.

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