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Rationalizing the Strength of Hydrogen-Bonded Complexes. Ab Initio HF and DFT Studies

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A comparative study of the relative stabilities of 17 multiply hydrogen-bonded complexes has been carried out using ab initio Hartree−Fock and density functional methods at the HF/6-311(d,p) and B3LYP/6-311-(d,p) levels, respectively. Predicted hydrogen-bond geometries, relative stabilities, solvent and structural effects, and electrostatic potential contours are discussed in conjunction with experimental data. The B3LYP method, which secures a better agreement of the optimized geometries with the available X-ray data, has also been applied to calculate the gas-phase free energies and enthalpies. The computations reveal that the frequently used incremental approach, which takes into consideration the primary and secondary electrostatic interactions, can often be deceptive in interpreting the stabilities of the multiply hydrogen-bonded dimers. The explanation that reduced entropy enhances the stability of dimers involving intramolecular hydrogen bonds in their monomeric parts compared to similar structures lacking such bonds has also been found to be misleading. A comparison of the calculated results with available experimental stabilities measured in $CHCl_3$ solutions shows that water present in the solvent may cause dramatic changes in relative stabilities. Electrostatic potential contours calculated at the B3LYP/6-311(d,p) level provide a useful qualitative explanation of the stability differences in the investigated complexes.

Introduction

Among noncovalent interactions,[1] hydrogen bonding[2] is of paramount significance. A vast variety of supramolecular assemblies owe their well-defined structure to the existence of adjacent hydrogen-bond-donor and -acceptor units at complementary constituent parts.[2,3] The investigation of hydrogen bonding is also important for many practical applications, such as the design of antibiotics[4,5] and the development of new materials with programmed properties, e.g., ordered nanocomposites,[5] photoresponsive sensors,[5,6] and hydrogen-bonded networks resulting in thin films[7] or liquid crystals.[8] Recent investigations in polymer science have shown that π-conjugated oligomers functionalized with units capable of hydrogen bonding can form reversible polymers[3,9] and stacked hierarchic structures.[10] These aggregates can be used in electrooptical devices such as solar cells[11] and light-emitting diodes[12] with tunable macroscopic properties. The ability to understand and predict the stability of hydrogen-bonded systems is of importance for the rational development of these chemical technologies. A number of experimental and theoretical methods have been applied for analysis of the hydrogen-bonded systems[2] to obtain simple reliable models for interpreting their stabilities. Bader's "atoms in molecules" theory that describes any chemical bond by partitioning its electron density[13] has been very seminal in formulating several models allowing the linear[14,15] and nonlinear[16−20] correlations between electron density at the bond critical point and bond distance and thus the bond strength. The groups of Elguero[19,20] and Mó[21−23] as well as other authors[24] have shown the usefulness of the latter models in interpreting the strength of some simple hydrogen-bonded systems such as methanol−water, phosphinic acid, and phosphinoxides and aminoxides. Another model that distinguishes primary and secondary electrostatic interactions (Figure 1) as a tool to predict hydrogen-bonding energies of complexes having more than one hydrogen bond in $CHCl_3$ solutions has been evolved on the basis of the Monte Carlo solution simulations by Jorgensen[25] and experimental studies by Schneider.[26] This concept has been widely applied and recommended as a useful guideline for interpreting stabilities and for designing new hydrogen-bonded associates.[3,27−31] Despite the lack of precise definition of a hydrogen bond, the statement that it is essentially of electrostatic nature[32] has been questioned by recent studies of low-barrier hydrogen bonds in enzyme catalysis[33,34] and theoretical remarks on the somewhat covalent nature of hydrogen bonding.[35] Recent experiments have also revealed a number of inconsistencies between the observed stabilities of hydrogen-bonded complexes in $CHCl_3$ solutions and values estimated considering solely primary and secondary electrostatic increments.[28,36−38]

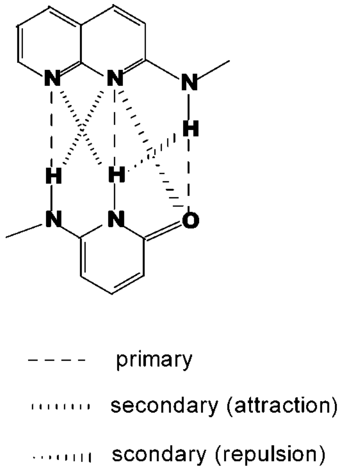

Figure 1. Primary and secondary electrostatic interactions in a hydrogen-bonded dimer as considered in the incremental approach.[13,14]

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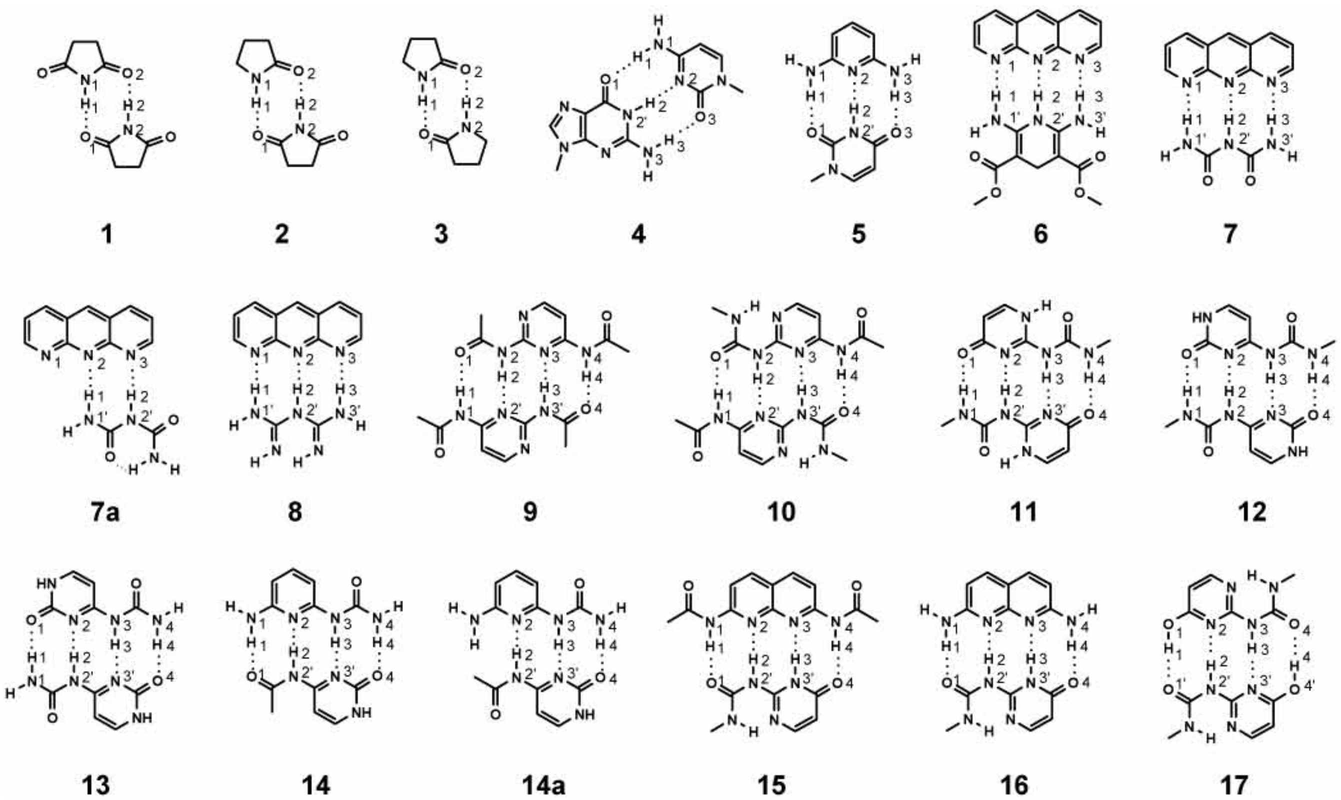
CHART 1



In this paper we test the hypothesis of secondary electrostatic interactions along with other rationalizations of stabilities of multiply hydrogen-bonded species by means of ab initio techniques. We also examine the applicability of the Hartree−Fock and the density functional theory calculations in the rational design of hydrogen-bonded building blocks. Ab initio calculations of 17 hydrogen-bonded dimers at the HF/6-311G(d,p) and B3LYP/6-311G(d,p) levels of theory have been carried out. The complexes investigated in this work are either experimentally studied[27,28,36,37,39] or plausible synthetic targets (Chart 1). The question of the nature of a hydrogen bond is not addressed in the present work. Hydrogen bonding will be discussed in terms of observable properties such as geometry, interaction energy, and electronic distribution. Earlier ab initio studies of the structures and stabilities of hydrogen-bonded assemblies of nucleic acid bases carried out in our group[40−47] show that quantum chemical techniques could now be used to perform calculations on molecular systems of practical significance.

Methods

The molecular geometries of hydrogen-bonded dimers **1**−**17** (Chart 1) have been fully optimized using both the Hartree−Fock theory (HF) and the density functional theory (DFT) with B3LYP functionals.[48] The standard 6-311G(d,p) basis set was used in all calculations. Literature analysis[45,47,49] shows that the geometries, relative stabilities, and frequencies of the structures calculated at the B3LYP/6-311G(d,p) level are in a good accord with experimental data. Pople et al. have shown that the absolute deviations for the bond lengths and angles are smaller than the corresponding values obtained at such levels of theory as MP2/6-31G(d) and QCISD/6-31G(d).[50] Our earlier studies of hydrogen bonding in nucleic acid bases indicate that the B3LYP method yields reliable interaction energies that correspond to the MP2/6-31G(d,p) level data.[41] Therefore, the B3LYP method was applied in the majority of calculations reported in this paper. The performance of the HF approximation with the 6-311G(d,p) basis set was also examined in this study, since it predicts similar stabilization energies for tetrads of nucleic acid bases[46,47] and is computationally less expensive. The interaction energies of the complex counterparts were estimated as the energy difference between the complex and the isolated components and were corrected for the basis set superposition error (BSSE). Electrostatic potential maps were calculated using cube=potential density=current keywords in the Gaussian input files and were visualized with the aid of the GOpenMol software.[51] The Gaussian 98[52] package of programs was used in the calculations. Structures **1**−**6**, **9**, and **10** have been optimized without any symmetry constraints, while C_s symmetry was assumed for all other complexes. Among the complexes optimized without symmetry restrictions, only dimers **5** and **6** exhibited remarkable deviations from planarity due to the pyramidal structure of their amino groups. Optimization of **6** assuming C_{2v} symmetry yielded structures with bigger interaction energies (by approximately 0.8 kcal/mol at the HF and DFT levels) and slightly larger values of the total energies (by 0.57 and 0.31 kcal/mol for HF and DFT, respectively) compared to the nonsymmetrical complex. Earlier investigations have revealed the pyramidal structure of the amino group in guanine complexes.[53] In this work we have also analyzed complex **4** composed of 9-methylguanine and 1-methylcytosine. Both HF and DFT calculations found the amino group in 9-methylguanine to be pyramidal in the isolated molecule and planar in the complex. However, Dannenberg et al. have noted that the planar structure of urea becomes the energy minimum after vibrational corrections.[54] For the sake of simplicity, we have assumed that the same would occur in complexes **7**, **8**, and **11**−**17**. Available X-ray data for derivatives of **11** and **17** prove the planar structures for these species in the solid state.[28] Complexes **9** and **10** were found slightly distorted from planarity in the solid state.[36] Our

TABLE 1: Comparison of Theoretical and Crystallographic[16,24] Data on Hydrogen-Bond Geometries (Å, deg) in Dimers 9−11 and 17

	data source	N2···N2 distance	N2−H1···N2 angle	N1···O1 distance	N1−H1−O1 angle
9	experimental	3.245	166	2.789	162
	HF/6-311G(d,p)	3.616	167	2.946	169
	B3LYP/6-311G(d,p)	3.409	170	2.821	168
10	experimental	3.239	171	2.748	169
	HF/6-311G(d,p)	3.546	169	2.902	169
	B3LYP/6-311G(d,p)	3.329	170	2.788	169
11	experimental	2.966	175	2.757	163
	HF/6-311G(d,p)	3.191	178	2.876	174
	B3LYP/6-311G(d,p)	3.013	179	2.784	173
17	experimental	2.980	173	2.580	169
	HF/6-311G(d,p)	3.221	170	2.697	172
	B3LYP/6-311G(d,p)	3.038	172	2.595	170

calculations yielded planar structures for these complexes. The latter result seems to be due to the simplified use of methyl substituents at the amino groups in the calculated dimers instead of *n*-butyl units present in experimentally studied compounds.[36] The HF and DFT level optimizations of **9** and **10**, applying C_{2h} symmetry, resulted in very close geometries and values of interaction energies as those obtained for the corresponding initially unsymmetrical structures. To verify the character of the optimized structures, calculations of their frequencies at the B3LYP/6-311G(d,p) level have been performed. All frequencies were found to be real except those reflecting inversion of NH_2 groups in the planar complexes **6**−**8**. The vibrational calculations allowed us to estimate the gas-phase enthalpies and free energies of the studied systems.

Results

The geometrical parameters of the hydrogen bonds of all the calculated complexes are collected in the Supporting Information. A comparison of the calculated hydrogen-bond geometries for structures **9**−**11** with available crystallographic results[28,36] is given in Table 1. Table 2 reports the calculated and available experimental interaction energies of the complexes. Analysis of hydrogen-bond geometries in the calculated structures reveals that the HF approximation results generally in longer hydrogen bonds and shorter N−H covalent bonds in comparison to the corresponding values of the DFT-optimized geometries. This indication is in line with published studies of nucleobase tetrads.[33,45] Table 1 indicates that the hydrogen-bond parameters in the species calculated by the DFT method are closer to the experimental solid-state geometries than the values obtained by the HF technique. Noticeable divergences of experimental and DFT calculated hydrogen-bond lengths occur for N−H···N bonds in dimers **9** and **10** (5% and 2.7%, respectively). In all other cases the deviations do not exceed 1.5%, reflecting, in general, a fairly good reproduction of the X-ray geometries. HF-optimized structures show essentially bigger deviations in hydrogen-bond lengths, amounting to 11% in the case of **9**. Both HF and DFT techniques showed similar trends in reproducing the hydrogen-bond angles. The deviations of the angles lie within 3.7% compared to the experimental geometries. The source of the discussed divergences of hydrogen-bond geometries may be attributed to a combination of two factors. First, as mentioned in the Methods section, the calculated structures are somewhat simplified analogues of the real systems. For instance, we have used methyl groups instead of long alkyl chains connected to urea units and omitted hydrocarbon substituents in pyrimidine rings. Second, as shown by Bickelhaupt et al.,[55] the molecular environment in the crystal cell may cause significant disagreement between theory and experiment regarding hydrogen-bond lengths.

Thus, due to the better agreement with experimental data and literature reports cited in the preceding section, the following discussion relies mostly on the DFT results. The longest hydrogen bonds (longer than 2.1 Å at the DFT level) correspond to N···H bonds present in dimers **6**−**10** and **12**−**14**, while the largest deviations of hydrogen-bond angles from 180° (<170° at the DFT level) manifest themselves in complexes **1**, **2**, **8**−**11**, and **15**. Interestingly, complexes **4** and **11**, which according to the calculations are the most strongly bound species among the triply and quadruply hydrogen-bonded systems, respectively, have also the shortest hydrogen bonds and almost straight hydrogen-bond angles. The shorter hydrogen bonds and the straight hydrogen-bond angles do not necessarily reflect stronger binding. For example, the thymine-2,6-diaminopyridine dimer, structure **5**, exhibits considerably less stability, despite short hydrogen bonds and small deviations from 180° for the corresponding angles. On the contrary, both **12** and **13**, with significantly high calculated interaction energies, display two long N···H hydrogen bonds and high deviations from 180° in the corresponding N−H···N angles.

As mentioned in the Introduction, there are several models evolved on the basis of Bader's theory showing linear or nonlinear relation between a bond length and electron density

TABLE 2: Available Experimental and Calculated Interaction Energies (kcal/mol) of the structures 1−17

dimer	refs	expl ΔG°_{298}	HF/6-311G(d,p): ΔE	B3LYP/6-311G(d,p) ΔE	$\Delta E_{PCM(CHCl_3)}$	ΔH°_{298}	ΔG°_{298}
1	13c	0.60	9.34	11.45	9.00	11.73	1.27
2	13c	1.20	10.59	13.32	9.98	13.38	2.72
3	13c	1.90	11.58	14.60	9.97	14.63	4.01
4	27a	6.80	24.32	28.14	19.20	25.94	15.29
5	27b	3.00	10.64	15.13	11.26	14.64	4.48
6	15	≥7	16.16	18.10	14.03	17.82	5.95
7			15.38	16.20	13.62	16.70	4.34
7a			15.65	17.03	12.62	16.98	7.01
8			13.50	14.43	12.73	14.47	4.72
9	24	3.00	18.00	21.03	13.47	22.02	6.35
10	24	7.20	20.33	27.09	15.78	29.96	8.73
11	16, 25	8.20−9.50	38.36	46.93	28.57	45.73	27.97
12			29.68	35.08	24.00	34.48	14.58
13			30.68	35.76	25.90	32.69	18.21
14			13.12	13.88	10.47	16.65	1.43
14a			9.31	10.97	6.46	11.38	3.33
15	25	≥10	24.20	30.39	19.89	33.20	16.10
16			25.75	32.78	25.94	31.10	18.28
17	16	7.68	24.57	32.78	23.00	30.67	16.44

at the bond critical point. The latter value in turn reflects the strength of the bond. Therefore, the hydrogen-bond lengths can be used to some extent as indexes of the stabilization energy per hydrogen bond. In this way we can perform analysis of some cooperative effects caused by multiple hydrogen-bonding linkages and compare the results with the concept considering primary and secondary electrostatic contributions. Thus, comparing dimers **1** and **3** there is logical shortening of the N−H···O bonds from 1.89 Å in **1** to 1.86 Å in **3** along with the increased stabilization energy on the latter complex. **2** has an intermediate value of Δ*E* (Table 2), but there is an unexpected elongation of N1−H1···O1 and shortening of N2−H2···O2 (1.94 and 1.80 Å respectively) bonds as compared both with **1** and **3**. Despite the fact that the N2−H2···O2 hydrogen bond in dimer **2** has two repulsive secondary electrostatic interactions, it is essentially stronger than N1−H1···O1 having only one such negative increment. Similarly, the hydrogen bond N1−H1···O1 in dimer **4** (1.77 Å) has only repulsive secondary interactions and is shorter and therefore stronger than two remaining linkages (1.92 and 1.91 Å), regardless of the attractive secondary forces that could be drawn for them. Complex **5** in turn exhibits its central hydrogen bond to be the shortest. Such examples clearly show the uselessness of the primary and secondary electrostatic increments. Analysis of hydrogen-bond lengths in dimers **7**−**17** is complicated because of their branched structures. Obviously, the covalent bond angles in these complexes could not be fully adjusted to fit well the equilibrium geometry of each hydrogen bond.

Therefore, the geometry analysis of the hydrogen bonds in the calculated assemblies gives useful insights into internal cooperative effects regarding the complex stabilities but at the same time provides no general rules for any qualitative or semiquantitative conclusions concerning the relative stabilities of the complexes. On the other hand the hydrogen-bond-geometry data could be profitable for the critical evaluation of a particular level of theory by comparing with proper care[55] the calculated and experimental molecular parameters.

Relative Stabilities and Solvent Effects. Table 2 indicates that both the HF and DFT techniques yield consistent trends in the description of interaction energies, Δ*E*, of the studied complexes. However, the stability order for the calculated structures in a vacuum does not agree well with the experimental trend. The evaluated ΔG°_{298} values also do not reproduce the experimental stability order in the $CHCl_3$ solutions. For example, complex **6**, reported to be the strongest among triply hydrogen-bonded systems in chloroform,[27] was calculated in a vacuum to be ~10 kcal/mol less stable than **4**. Similarly, the Δ*E* values of the complexes **10** and **15** are underestimated compared to that of **4**, despite the greater strengths of the former dimers observed in chloroform. One obvious reason for this difference is that the interaction energies of the structures optimized in a vacuum should not be compared directly with the experimental stabilities measured in chloroform solutions. To account for the plausible solvent effects causing the differences in relative stabilities of the complexes under investigation, the following studies have been performed.

(a) Evaluation of the Interaction Energies of the Complexes Applying the PCM Chloroform Model at the B3LYP/6-311G(d,p) Level of Theory (Table 2). An analysis of the interaction energies obtained with the PCM chloroform model shows a mostly linear decrease in the corresponding values computed for the structures in a vacuum. Therefore, low-polar chloroform should produce virtually no effect on the stability order within the considered series of complexes. However, under experimental conditions chloroform always contains a considerable amount of water that could affect the stabilities of hydrogen-bond complexes. For instance, Jorgensen et al.[56] have demonstrated an elegant theoretical explanation of the water effect in suppressing the interaction of fluorine anion with the bis(phenylurea) calix[4]arene receptor in chloroform.

(b) Study of the Water Effect. An analysis of the water influence on the interaction energies has been carried out in two ways. First, the PCM water model was applied, and the stabilities of selected structures were evaluated. As mentioned above, the interaction energies obtained for complexes **4** and **6** in a vacuum differ by about 10 kcal/mol (Table 2), yielding the former complex more stable. The introduction of the chloroform PCM model reduces the energy gap to 5 kcal/mol. The PCM water model resulted in interaction energies that are equal to −8.1 and −9.0 kcal/mol for complexes **4** and **6**, respectively, in agreement with the experimental trend. The stability order of very similar dimers **11** and **12**, which differ in a vacuum by about 10 kcal/mol, is also reversed when the PCM water model is applied revealing interaction energies of −12.7 and −14.8 kcal/mol, respectively. However, the PCM water model results should be taken with caution, since there are experimental[57,58] and theoretical[59,60] evidences indicating that the association of nucleic acid bases in water leads to stacked dimers rather than to hydrogen-bonded complexes.

In an alternative approach, we have analyzed the influence of water molecules modeled by explicit inclusion of their interactions with selected complexes. Since the quantum chemical calculations with large basis sets are still time-consuming, we concentrated on the detailed studies of complexes **4** and **6** and their components due to the largest inconsistencies between calculated and measured stabilities of the latter complex. Figure 2a shows the B3LYP/6-311G(d,p)-optimized structures of **4** and **6** interacting with two water molecules. Here, in agreement with similar studies,[43,44] the hydration water has only a marginal effect on the interaction energy between the two main constituent parts of the complex. Complexes of the isolated components of **4** and **6** with water and the corresponding interaction energies are depicted in Figure 2b. Obviously, both components of **4** interact with water molecules more efficiently than do the monomers of **6**. The latter observation seems to indicate that under experimental conditions the overall stability of **4** is diminished by the presence of water to a greater degree in comparison to complex **6**, making an interpretation of the greater experimental stability of **6**[27] in comparison to **4** on the basis of favorable secondary electrostatic interactions misleading.

Structural Effects Affecting Stabilities. Apart from the solvent effects, the influence on the stability of structural parameters such as hydrogen-bond-donor−acceptor sequences, specific substituents, and conformations is notable. For instance, complexes **9** and **10**, which differ by only one group not participating in hydrogen bonding, exhibited remarkable variation in their stabilities both in calculated and experimental[36] studies. It should be stressed that the unexpectedly high experimental stability of **10**, having all secondary electrostatic interaction unfavorable, was the first evidence against the incremental approach.[25,26] Dimer **17**[28] with alternating donor and acceptor sites was shown to be even more stable than **10**.[36] Meijer et al.[28,36] explained the observed phenomenon by significant entropy compensation in **10** and **17** due to intramolecular hydrogen bonds in the corresponding monomers, but the necessary thermodynamic studies have not been undertaken. However, our computations (Table 2) show that the differences ΔΔ*E* in the HF and DFT interaction energies between **9** and

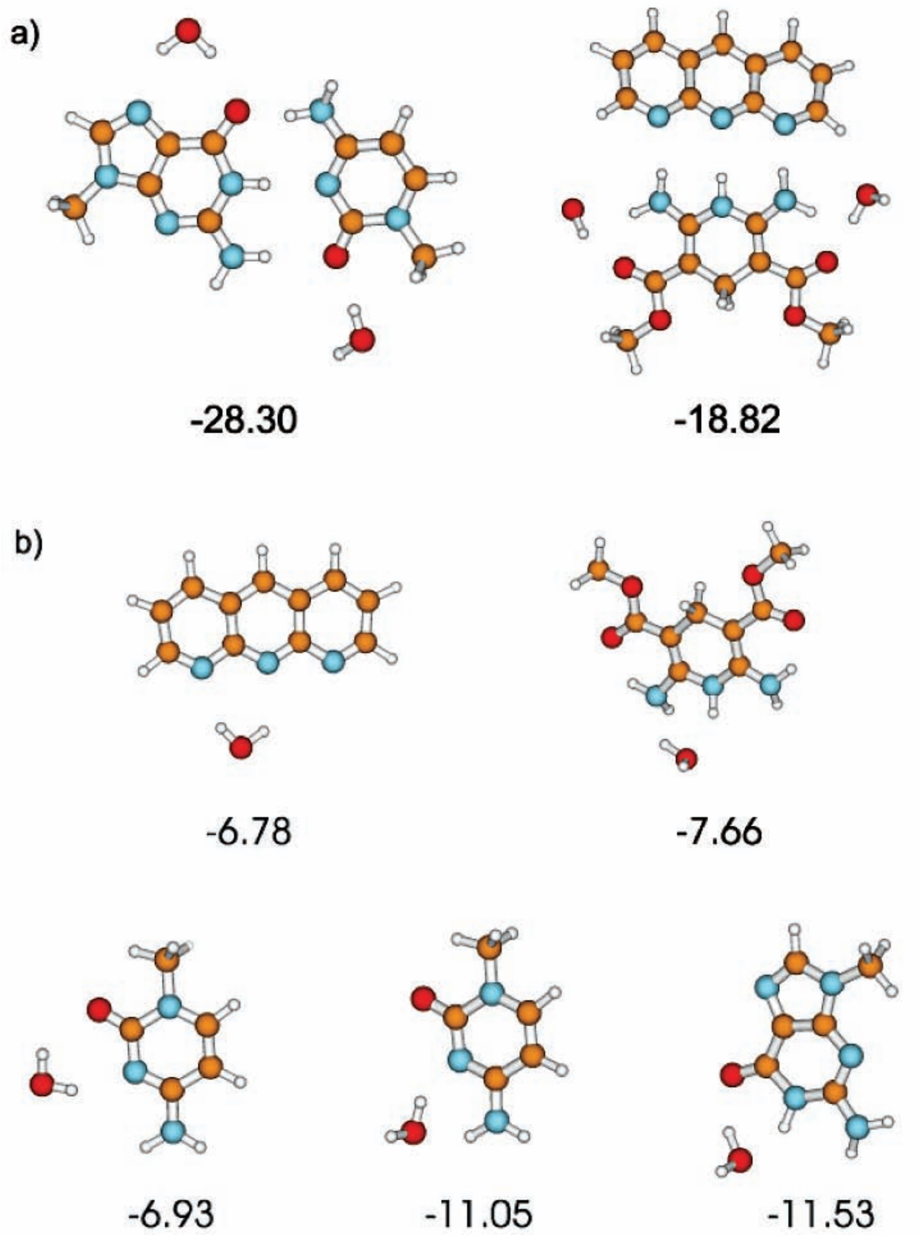


Figure 2. Influence of explicit water molecules on hydrogen-bond association. (a) B3LYP/6-311G(d,p)-optimized structures of complexes **4** and **6** involving water molecules. Numbers given below the structures correspond to the interaction energies (ΔE, kcal/mol) of the complexes. (b) B3LYP/6-311G(d,p)-optimized structures and interaction energies (ΔE, kcal/mol) of isolated components of complexes **4** and **6** with water molecules.

10 are in line with the experimental trend revealing the enthalpy as the stabilizing component. Moreover, evaluation of ΔH°_{298} and ΔG°_{298} for the gas-phase complexes (Table 2) reveals the larger entropy component in **10** compared to **9**. The HF and DFT calculated $|\Delta\Delta E|$ differences between the quasi-twins **11** and **12** are even larger. In this case, the entropy favors **11**, a dimer with intramolecular hydrogen bonds. Unfavorable conformations of diurea in **7** and cytosine derivative in **14** and, consequently, unfavorable entropy result in the larger $|\Delta G^\circ_{298}|$ values of their stereoisomers **7a** and **14a**, respectively, despite the reduced number of hydrogen bonds. Therefore, the latter example can be an illustration of entropy-driven stabilization in hydrogen-bonded complexes. The fact that complexes **7**, **12**, and **14** have not been studied experimentally suggests them as interesting benchmarks for experimental chemists.

For a better understanding of intermolecular interactions in the hydrogen-bonded complexes, electrostatic potentials have been calculated and visualized for selected structures. The electrostatic potential has proved to be particularly useful in rationalizing the interactions between molecules and molecular recognition processes.[61] For instance, strong electrostatic repulsions between electronegative carbonyl groups that are located in close proximity in the complexes **1**−**3** as depicted in Figure 3 seem to be responsible for the steady decrease in the interaction energies in the sequence of dimers lactam−lactam **3**, lactam−imide **2**, and imide−imide **1**. This trend within the series of complexes **1**−**3** represents the simplest example when relative stabilities could be at least qualitatively explained in terms of unfavorable secondary electrostatic interactions.[25] Using the calculated ΔG°_{298} values, one can even deduce increments of 3.3 and 1.3 kcal/mol for primary and secondary interactions in dimers **1**−**3**. However, none of the remaining complexes, with the accidental exception of **5**, satisfy this incremental rule. Such consideration along with the discussion about hydrogen-bond lengths given in the beginning of this section cast additional inconsistencies in the electrostatic increments approach.

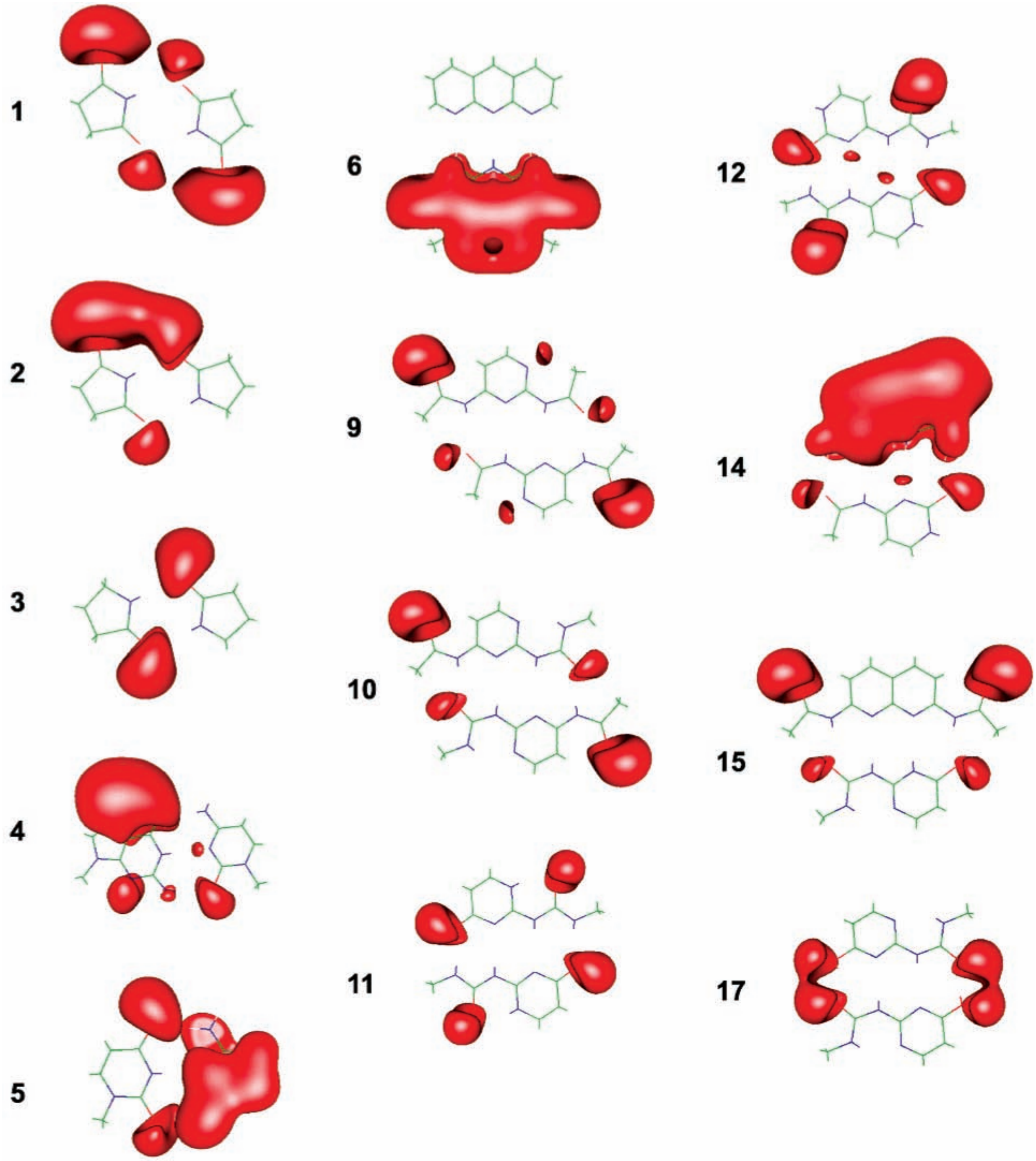


Figure 3. Electrostatic potential contours of selected complexes. (The negative contour spacing in the figure is −0.03 au.)

Intermolecular interactions within triply and quadruply hydrogen-bonded associates are more complex. The uracil−diaminopyridine pair **5** also exhibits unfavorable electrostatic interactions. However, in the latter case the main disadvantageous interactions originate unexpectedly from repulsions between the carbonyl and amino groups (Figure 3). Dimer **4** shows a complicated contour of the negative electrostatic potential with all intermolecular contacts favorable due to the outlying carbonyl groups. Complexes **6**−**8**, which have in their structures identical bonding patterns with hydrogen-bond donors and acceptors positioned on different parts of the complexes, demonstrate comparable stabilities that decrease from **6** to **8**. For simplicity, components **6**−**8** could be referred to as "donor part" and "acceptor part". Surprisingly, an analysis of the negative electrostatic potential contour of **6** depicted in Figure 3 shows that the "donor part" of the complex is actually an extremely electronegative component. Charge transfer should be taken into account as a possible mechanism stabilizing structures **6**−**8**.

At a glance, the electrostatic potential contours drawn for quadruply hydrogen-bonded pairs of dimers **9**, **10** and **11**, **12** are not very revealing. Nevertheless, constituent parts of complexes **9** and **10** resembling 2,6-diaminopyridine derivatives can roughly be compared with the parent 2,6-diaminopyridine present in complex **5**. It is clear that, contrary to 2,6-diaminopyridine, the negative charge in the monomers of **9** and **10** is mostly located on the carbonyl moieties. Another 2,6-diaminopyridine analogue is part of **14**, the weakest among quadruply bound complexes. As mentioned above, complexes **10** and **11** having in their monomeric parts intramolecular hydrogen bonds show significantly larger stabilities than complexes **9** and **12**, respectively. This phenomenon seems to occur due to through-space electron withdrawing from the ring by adjacent carbonyl groups. A decrease in the value of the negative electrostatic potential on the heterocyclic nitrogen atoms in **9** and **12** in regard to **10** and **11** respectively (Figure 3) supports this explanation. Repulsions between oxygen atoms of carbonyl and hydroxyl groups forming two OH···O hydrogen bonds in **17** destabilize this dimer in comparison to its tautomer **11**. Generally, the considered contours of negative electrostatic potential indicate that the carbonyl group (if present) often has the largest stabilizing or destabilizing influence on the interaction energy of a hydrogen-bonded associate.

Besides the electrostatic potential contours, one can simply compare the interaction energies of similar species with and without certain substituents. For example, substituents at the amino groups exhibit a decreasing effect on the calculated stability of a complex. Thus, the elimination of two acetyl groups in **15** transforms it to **16**, that is, ca. 2 kcal/mol more stable both in HF and DFT approximations in a vacuum. Interestingly, the calculated ΔH and ΔG values reflect growing entropy in **15** compared to **16**. Therefore, despite the fact that the enthalpy of hydrogen bonding in **15** is larger than that in **16**, the overall process is entropically disfavored. The reduced free energy of the complex formation upon amines acetylation contradicts experimental studies of complexes with 2,6-diaminopyridine and its *N*,*N*′-diacetylated derivative.[62] The latter compound was shown to form stronger complexes with *N*-propylthymine than parent 2,6-diaminopyridine. The methylation of amino groups in **13** also increases entropy, reflecting less effective hydrogen bonding in **12**.

Conclusions

A number of hydrogen-bonded complexes have been analyzed to test both the applicability of the secondary interactions principle and the application of ab initio calculations in the design of potentially strong and selective hydrogen-bonded associates. The results of our calculations indicate that the incremental approach considering primary and secondary electrostatic contributions to a hydrogen bond cannot be trusted. Other simplified rationalizations of experimental stabilities, e.g., in ref 24, should also be avoided. The present study shows that the stability information of a single complex could not be directly used to obtain stability data for hydrogen-bonded assemblies in general. It is noteworthy that the geometry analysis of the hydrogen bonds can give useful insights into their cooperative effects affecting the complex stabilities. The hydrogen-bond-geometry data could be profitable for the critical evaluation of a particular level of theory by comparing the calculated and experimental molecular parameters. We have also shown that a solvent may cause dramatic effects on the complex relative stabilities that cannot be foreseen by the electrostatic increment approach. The calculated electrostatic potential maps prove to be useful in rationalizing interactions between hydrogen-bonded complex components. Finally, we believe that the growing performance of ab initio methods may offer certain advantages in the rational design of new materials in the future.

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Supporting Information Available: The geometrical parameters of the hydrogen bonds of all the calculated complexes. This material is available free of charge via the Internet at http/::pubs.acs.org.

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