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Reply to Comment on "Rationalizing the Strength of Hydrogen-Bonded Complexes. Ab Initio HF and DFT Studies"

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In 1989, Schneider et al. suggested a *free energy increment per hydrogen bond* method for predicting the stability of bimolecular complexes involving selected amides and barbiturates.[1] Two years later, on the basis of the Monte Carlo dynamics simulation, Pranata et al.[2] introduced a more sophisticated incremental scheme for hydrogen-bonded species that divides the intermolecular contacts into primary and secondary electrostatic interactions. According to the latter idea, the secondary electrostatic interactions could be attractive or repulsive, depending on the sequence of hydrogen-bond donors (D) and acceptors (A) in the constituent parts of the complex. In 1996, Sartorius and Schneider[3] reported comprehensive experimental NMR studies of hydrogen-bonded dimers that support the incremental approach of Pranata et al.

Critical evaluation of these approaches by means of modern ab initio techniques was the focus of our paper.[4] It was recently shown that in many cases (e.g., the empirical $\pi-\pi$ ("sandwich") interaction model of aromatic stacking[5]) the simplified theory was not confirmed by detailed ab initio studies that provide reliable information concerning the geometries and energies of the studied species. Prior to the detailed reply to the comments of Schneider, we would like to mention some general drawbacks of the primary and secondary interactions principle. It is noteworthy that interpreting the stabilities of hydrogen-bonded complexes by electrostatic increments contradicts modern well-founded experimental and theoretical findings regarding the nature of hydrogen bonding. It is now commonly accepted that hydrogen bonding is not solely of electrostatic nature (e.g., refs 32−35 in our paper[4]), and the results of hydrogen-bond energy decomposition reveal that the electrostatic contribution covers only 40−70% of the total interaction energy. Another general weak point of the incremental approach is its inconsistency with Bader's "atoms in molecules" theory. In our article, we mentioned that in several cases the strongest hydrogen bonds (i.e., the shortest according to Bader's theory) were surrounded only by repulsive secondary electrostatic interactions. One more issue casting doubts is the first incremental rule in which the value of 5 ± 0.5 kJ/mol had been selected as an average contribution per one hydrogen bond without any partitioning into primary and secondary components. Interestingly, this value has also been shown to reproduce the stabilities of selected complexes.

Following is our response to the issues that have been raised in the comments of Schneider.

While to establish new empirical rules many examples are necessary to prove such a development, it is enough to provide only one case that does not agree with the theory to doubt it. Our paper provides certainly more than one such example. Therefore, despite the fact that free energy increments of 7.9 and 2.9 kJ/mol for primary and secondary electrostatic interactions, respectively, have been shown to satisfy the stabilities of 58 complexes,[3] the number of considered species does not seem to play a major role, because previously Pranata et al.[2] deduced very similar incremental values (7.5 and 2.5 kJ/mol) considering only two complexes. The complexes described by Sartorius and Schneider[3] are built up from structurally similar units incorporating amide, amine, and pyridine blocks for which the presence of water traces may cause systematic errors. In our paper,[4] we have revealed that water was bound by an AD combination, which is twice as strong as being bound by AA or DD combinations, which significantly weaken the former type of complex (exemplified by complexes **4** and **6** in our article[4]). We also referred to a similar theoretical explanation (role of traces of water) concerning the strongest binding of the fluorine ion predicted by ab initio study that is in contrast to its experimentally determined weak complexation by a urea receptor.[6] Among the complexes considered in our paper, the available experimental data demonstrated a satisfactory agreement with the incremental approach for complexes **1**−**6** and **9**. Our structure **9** possessing an ADAD combination indeed contains a *cis-amide* unit that is a destabilizing conformation according to Schneider's comment. However, the conformational destabilization within a single unit gains some energy in the bimolecular complex **9**, the structure of which was proved by X-ray analysis.[7] Moreover, Schneider has not noticed the fact that the experimental energy of complex **9** is reproduced fairly well if the empirical primary and secondary increments are applied. Complex **10** contains the hydrogen-bonding pattern of **9** and has been found to be much more stable than **9** by both experiment and our calculations, raising serious doubts about the incremental approach. Complex **17** contains hydroxyl groups as donors that, according to argument of Schneider, cannot be analyzed by the increments. We consider this as one more failure for the Sartorius and Schneider paper, which is titled "A General Scheme Based on Empirical Increments for the Prediction of Hydrogen-Bond Associations of Nucleobases and of Synthetic Host−Guest Complexes." The incremental scheme is certainly not of general applicability. It can interpret the stabilities only of a limited type of hydrogen-bonded species with a variety of exceptions. On the contrary, our study demonstrates that the geometries, energies, and various factors influencing the stabilities of hydrogen-bonded complexes could be efficiently analyzed applying ab initio techniques.

Our calculations reveal the marginal chloroform effect that proportionally diminishes the stabilities of all complexes compared to the vacuum structures. We do not see any controversy with the relevant experimental data in this respect. The stability order in the calculated complexes remained the same after applying the PCM chloroform model, which was in a good accord with the experimental statements correctly mentioned by Schneider. Our representative B3LYP/6-311G-(d,p) calculations involving the carbon tetrachloride PCM model for complex **1** show a reasonably higher stabilization energy (ΔE = 10.40 kcal/mol, previously unpublished) than that calculated for the chloroform model (ΔE = 9.00 kcal/mol). Other calculated solvent effects were also carefully discussed in our paper showing that the most spectacular effect was caused by the inclusion of explicit water and seemed to be responsible for most of the inconsistencies found between the calculated and experimental complex stabilities.

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We believe that the application of the B3LYP/6-311G(d,p) level of theory is well justified in our paper.[4] Molecular geometries and interaction energies of various hydrogen-bonded complexes obtained at this level are exceptionally close to the available values calculated using the MP2 electron correlation method, as well as to the experimental data on gas-phase enthalpies for selected nucleobase dimers.

It should be stressed that our concern is also related to the short-sighted use of the incremental approach by other authors. For example, a recent review by Sherrington[8] simply advertises without proof the incremental scheme, while in another paper, the authors apply the secondary interactions to rationalize even intramolecular hydrogen bonds.[9] In summary, we hope that this debate will facilitate the routine application of reliable ab initio studies to verify the applicability of empirical rules.

References and Notes

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