Comment on “Rationalizing the Strength of Hydrogen-Bonded Complexes. Ab Initio HF and DFT Studies”

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A recent paper by O. Lukin and J. Lesczynski in *The Journal of Physical Chemistry A*[1] addresses the important question of whether the stability of the hydrogen-bond complexes with amide-type donors and acceptors in solution can be predicted by empirical parameters derived from experimental studies and whether ab initio calculations perform significantly better in this context. The authors come to conclusion that “The results...indicate that the incremental approach considering primary and secondary electrostatic interactions can not be trusted.” and that the rationalization of hydrogen bonding in nucleobase-related complexes with secondary interactions as proposed on the basis of electrostatics by Jorgensen et al.[2] is insufficient, particularly with respect to solvent effects. In view of the paramount significance of such hydrogen bonds in biological systems such as nucleic acid components, as well as in synthetic supramolecular complexes, in drug design, for new materials, and other applications, the strategy and conclusions of Lukin and Lesczynski deserve several comments. It should be borne in mind that empirical parameters such as ours[3]are free from any mechanistic assumptions and, in contrast to the calculations by Jorgensen et al.,[2] are not restricted to consideration of electrostatic effects.

One crucial question point is the agreement obtained with empirically derived free energy increments, which in our 1996 paper[3] has been shown to reproduce 58 different complexes observed in chloroform solution within ±0.4 kcal/mol of the free energy; in contrast, the molecular orbital calculations[1] were compared to only 11 complexes and generally yielded worse, if any, agreement (see below). It should be noted that the stability of 7 of these 11 complexes is well predicted by empirical increments, and the remaining 4 others are fraught either with (i) severe experimental difficulties due to their small stability (complex **1** and **2** in the paper by Lukin and Lesczynski) or by (ii) the need to build up a destabilizing cis-amide conformation (complexes **9**, **10**, **15**, and **17**), or by (iii) introduction of hydroxy functions instead of amide groups (complex **17**; in addition, the presence of tautomeric forms with pyrimidinone instead of hydroxy pyrimidine structures must be considered[4]). As pointed out by a reviewer, the neglected tautomeric forms can interfere in particular with all ureidopyrimidones.

The most serious concern in dealing with hydrogen-bond energies is their dependence on the reaction medium. Lukin and Lesczynski conclude that calculations showed the marginal chloroform effect proportionally diminishing stabilities of all the complexes compared to the vacuum structures. This is in disagreement with experimental studies. Chloroform is a quite acidic solvent, as described in all empirical hydrogen-bond donor parameter scales[5] and by analyses of vibrational spectra[6] or of crystallographic databases[7] Under the usual measuring conditions, the molar concentration of chloroform is about 10^4 times higher than that of the solute. In carbon tetrachloride, amide-type hydrogen-bond dimers can therefore show an increase by a whole order of magnitude,[8] even though such perhalogenated systems also have sizable hydrogen-bond acceptor capacity[9] and thus are expected to be smaller than gas-phase values. Lukin and Lesczynski have applied B3LYP/6-311G(d,p) calculations to account for the solvent effect of chloroform with ΔG values sometimes coming closer to the experimental energies but, in other cases, showing large discrepancies (such as for dimer **4** 15 (calcd) vs 6.8 (exptl) kcal/mol; for dimer **11** 28 (calcd) vs 9 (exptl) kcal/mol; for dimer **17** 16.4 (calcd) vs 24.5 (exptl) kcal/mol). The discrepancies were suspected to be due partially to the presence of water in chloroform, the influence of which was evaluated with a PCM model and with B3LYP/6-311G(d,p) calculations including two water molecules, still leading to large discrepancies to the experimental data but to a more correct stability sequence for the two dimers studied this way. Here, it should be noted that water in chloroform on related hydrogen-bonded complexes has been shown to affect ΔG insignificantly and ΔH and ΔS in a compensating manner[10] with, however, significant variations with the underlying structures.[11] Calculations on water effects should also take into account its self-association observed in chloroform.[12]

There is no reason to assume that the medium effects cannot be rationalized just by competition of the excess solvent molecules. Methanol, as a much stronger hydrogen-bond donor, lowers association constants of nucleobase analogues even at concentrations in chloroform as low as 1% by a factor of magnitude.[8] Significant progress in ab initio calculations have been made also by inclusion of polarization and electron correlation functions,[13] but much needs to be done before they can predict stabilities as well as empirically derived descriptors. Entropic effects can play a major role in the association of larger solute molecules; the effect of flexible single bonds in hydrogen-bonded complexes can again be quantified from the analysis of experimental data sets.[14]

References and Notes

(1) Lukin, O.; Lesczynski, J *J. Phys. Chem. A* **2002**, *106*, 6775.

(2) Pranata, J.; Wierschke, S. G.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1991**, *113*, 2810. See also: Houk, K. N.; Li, Yi. *Chemtracts: Org. Chem.* **1992**, *5*, 40.

(3) Sartorius, J.; Schneider, H.-J. *Chem.—Eur. J.* **1996**, *2*, 1446.

(4) MacPhail, R. A.; Williams, L. D.; Jones, D. A.; Shaw, B. R. *J. Biomol. Struct. Dyn.* **1992**, *9*, 881.

(5) Abraham, M. H. *Chem. Soc. Rev.* **1993**, *22*, 73. Raevsky, O. A. *Russ. Chem. Rev. (Engl. Transl.)* **1990**, *59*, 219 and references therein.

(6) Daniel, D. C.; McHale, J. L. *J. Phys. Chem. A* **1997**, *101*, 3070. Tsymbal, I. F.; Ryl’tsev, E. V.; Boldeskul, I. E.; Lisak, B. G. *Khim. Fiz.* **1993**, *12*, 988. (CA *119:*236829; AN **1993**:636829).

(7) Steiner, T. *New J. Chem.* **1998**, *22*, 1099.

(8) Schneider, H.-J.; Juneja, R. K.; Simova, S. *Chem. Ber*. **1989**, *112*, 1211.

(9) Abraham, M. H.; Enomoto, K.; Clarke, E. D.; Sexton, G *J. Org. Chem.* **2002**, *67*, 4782.

(10) Adrian, J. C., Jr.; Wilcox, C. S. *J. Am. Chem. Soc.* **1991**, *113*, 678.

(11) Adrian, J. C., Jr.; Wilcox, C. S. *J. Am. Chem. Soc.* **1992**, *114*, 1398.

(12) Eblinger, F.; Schneider, H.-J. *J. Phys. Chem.* **1996**, *100*, 5533 and references therein.

(13) Hobza, P.; Sponer, J. *Chem. Rev.* **1999**, *99*, 3247. Sponer, J.; Leszczynski, J.; Hobza, P. *J. Mol. Struct. (THEOCHEM)* **2001**, *573*, 43. Sponer, J.; Hobza, P. *J. Phys. Chem. A* **2000**, *104*, 459 and references therein.

(14) Eblinger, F.; Schneider, H.-J. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 826.

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