

π -Stacked Quadruply Hydrogen-Bonded Dimers: π -Stacking Influences H-Bonding

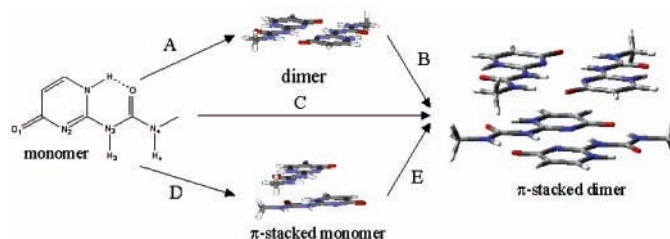
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ABSTRACT



The effects of π -stacking on the stability of multiply hydrogen-bonded systems are investigated using hybrid DFT calculations on π -stacked quadruply H-bonded dimers of ureidopyrimidinone in its different tautomeric forms. Both the strengths of the hydrogen bonds and the relative occurrence of tautomers are influenced by π -stacking; electrostatics and natural bond orbital analysis are used to explain these observations. Finally, these conclusions are independent of the precise nature of the multiply hydrogen-bonded systems, including the DNA base pairs.

Recently, the development of new materials displaying multiple hydrogen bonds (H-bonds) has attracted significant attention.¹ Specifically, the development of highly stable dimers with four^{1c,2} or more³ H-bonds per dimer is of relevance, given the larger number of H-bonds in comparison

to, e.g., DNA. The ability to understand and predict the stability of H-bonded systems is important, e.g., for the rational development of supramolecular polymers.⁴ H-bonded dimers have also been the topic of extensive theoretical investigations,⁵ including analyses by natural bond orbital (NBO) theory.⁶ Multiply H-bonded systems, including the DNA base pairs,⁷ have also been studied theoretically, particularly in order to rationalize relative dimer stabilities with primary and secondary electrostatic interactions between donor and acceptor sites.⁸

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(1) (a) Zimmerman, S. C.; Corbin, P. S. *Struct. Bonding* **2000**, *96*, 63. (b) Sherrington, D. C.; Buggy, M. *Chem. Soc. Rev.* **2001**, *30*, 83. (c) Sijbesma, R. P.; Meijer, E. W. *Chem. Commun.* **2003**, 5.

(2) (a) Sijbesma, R. P.; Beijer, F. H.; Brunsveld, L.; Folmer, B. J. B.; Hirschberg, J. H. K. K.; Lange, R. F. M.; Lowe, J. K. L.; Meijer, E. W. *Science* **1997**, *278*, 1601. (b) Corbin, P. S.; Zimmerman, S. C. *J. Am. Chem. Soc.* **1998**, *120*, 9710. (c) Zhao, X.; Wang, X.-Z.; Jiang, X.-K.; Chen, Y.-Q.; Li, Z.-T.; Chen, G.-J. *J. Am. Chem. Soc.* **2003**, *125*, 15128 and references cited therein.

(3) (a) Zeng, H.; Miller, R. S.; Flowers, R. A., III; Gong, B. *J. Am. Chem. Soc.* **2000**, *122*, 2635. (b) Bisson, A. P.; Carver, F. J.; Eggleston, D. S.; Haltiwanger, R. C.; Hunter, C. A.; Livingstone, D. L.; McCabe, J. F.; Rotger, C.; Rowan, A. E. *J. Am. Chem. Soc.* **2000**, *122*, 8856. (c) Corbin, P. S.; Zimmerman, S. C.; Thiessen, P. A.; Hawryluk, N. A.; Murray, T. J. *J. Am. Chem. Soc.* **2001**, *123*, 10475.

(4) (a) Brunsveld, L.; Folmer, B. J. B.; Meijer, E. W.; Sijbesma, R. P. *Chem. Rev.* **2001**, *101*, 4071. (b) Cifferi, A., Ed. *Supramolecular Polymers*; Marcel Dekker: New York, 2000.

(5) Hadži, D. *Theoretical Treatments of Hydrogen Bonding*; Wiley: New York, 1997.

(6) (a) Caminati, W.; Melandri, S.; Moreschini, P.; Favero, P. G. *Angew. Chem., Int. Ed.* **1999**, *38*, 2924. (b) Kryachko, E. S.; Huyskens, T. Z. *J. Phys. Chem. A* **2001**, *105*, 7118. (c) Pepov, L. *Chem. Phys.* **2002**, *285*, 177.

(7) (a) Fonseca Guerra, C.; Bickelhaupt, F. M. *Angew. Chem., Int. Ed.* **2002**, *41*, 2092. (b) Asensio, A.; Kobko, N.; Dannenberg, J. J. *J. Phys. Chem. A* **2003**, *107*, 6441 and references cited therein.

More recently, the experimental study of multiply H-bonded dimer systems has been extended to π -stacked systems.^{4a,9} Since the combination of π -stacking and multiply H-bonded systems is of significant importance, both in biology and in materials science, theoretical investigations are of interest. The current paper presents, to the best of our knowledge, the first results on the effects of π -stacking on multiple H-bond formation and concentrates on π -stacked quadruply H-bonded dimers of ureido-4[1*H*]-pyrimidinone (further, keto isomer **1k**) and its enol isomer, pyrimidin-4-ol (further, enol isomer **1e**); see Figure 1. In addition, the

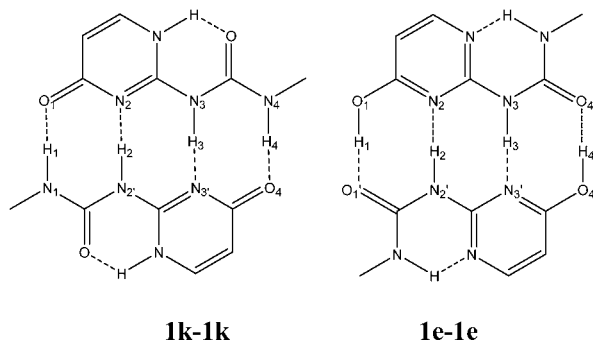


Figure 1. Quadruply H-bonded dimers under study.

computations explain the hitherto surprising observation that in π -stacked dimers the enol content is about an order of magnitude higher than can be explained from the (small) equilibrium constants for tautomerization $\mathbf{1k} \rightleftharpoons \mathbf{1e}$ ^{9b,10} and shed light on the effects of π -stacking on the H-bonding in DNA.

To locate the minimum on the potential energy surface¹¹ for π -stacked keto isomers, the dimer structure was first optimized at the B3LYP/6-31G(d,p) level of theory¹² and used as such for a grid of single-point calculations. In this

(8) (a) Jorgensen, W. L.; Pranata, J. *J. Am. Chem. Soc.* **1990**, *112*, 2008. (b) Lukin, O.; Lezczynski, J. *J. Phys. Chem. A* **2002**, *106*, 6775.

(9) (a) Schenning, A. P. H. J.; Jonkheijm, P.; Peeters, E.; Meijer, E. W. *J. Am. Chem. Soc.* **2001**, *123*, 409. (b) ten Cate, A. T.; Dankers, P. Y. W.; Kooijman, H.; Spek, A. L.; Sijbesma, R. P.; Meijer, E. W. *J. Am. Chem. Soc.* **2003**, *125*, 6860.

(10) (a) Folmer, B. J. B.; Sijbesma, R. P.; Kooijman, H.; Spek, A. L.; Meijer, E. W. *J. Am. Chem. Soc.* **1999**, *121*, 9001. (b) Hirschberg, J. H. K. K.; Koevoets, R. A.; Sijbesma, R. P.; Meijer, E. W. *Chem.—Eur. J.* **2002**, *9*, 4222.

(11) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*, revision B3; Gaussian, Inc.: Pittsburgh, PA, 2003.

grid the π -stacking distance R between the centers of the two dimers, the rotation of two π -stacked dimers Θ , and the translational sliding (X,Y) of the π -stacked dimers were varied for stacked keto dimers (**1k-1k/1k-1k**), stacked enol dimers (**1e-1e/1e-1e**), and a heterostack of keto and enol dimers (**1k-1k/1e-1e**). The results for Θ and (X,Y) are shown in Figure 2 for **1k-1k/1k-1k**. One clear minimum was found

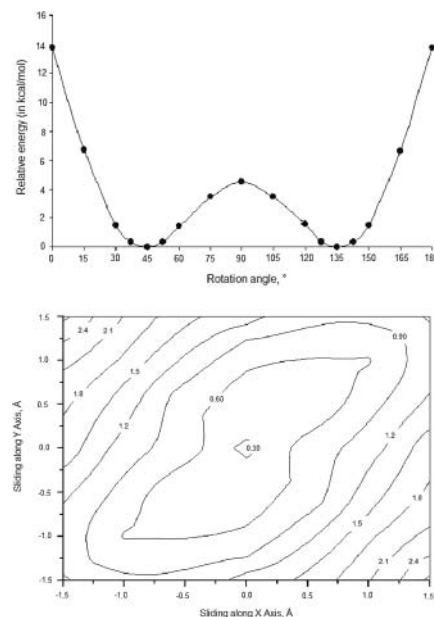


Figure 2. Location of minimum of π -stacked keto dimers **1k-1k/1k-1k** [B3LYP/6-31G(d,p) computations].

for each of the three systems. The thus obtained lowest energy geometries were used as starting points for full geometry optimizations. The resulting optimized structures are depicted in Figure 3, together with their values of R , Θ , and (X,Y). Only for **1k-1k/1k-1k** are the geometries of comparable experimental systems available. In those cases, the experimental hydrogen-bonding distances $r(\text{N}_2-\text{N}_2)$ and $r(\text{N}_1-\text{O}_1)$ are 2.97 and 2.76 Å,¹³ respectively, while the computed values are 3.01 and 2.78 Å, respectively. The π -stacking distance R in the stacked dimer was measured to be 3.55 Å,^{9b} while the computed value is 3.56 Å. Finally, ΔG in “solution” (PCM model mimicking CHCl_3) was computed to be -11.29 kcal/mol at 298 K, while the experimental value was measured to be -12.1 kcal/mol.¹⁴ Since agreement with experiment within experimental error is found for all these parameters, this validates our method.

(12) (a) Agreement with experimental data and similarity between B3LYP, MPW1B95, B98, and local MP2 data (vide infra) strongly suggest that none of our conclusions are qualitatively affected by the method used. Quantitatively correct data await the applicability of more advanced methods such as CCSD(T). (b) For B3LYP studies of systems with a significant dispersion component: Zuilhof, H.; Morokuma, K. *Org. Lett.* **2003**, *5*, 3081. (c) Reha, D.; Kabelác, M.; Ryjáček, F.; Šponer, J.; Šponer, J. E.; Elstner, M.; Suhai, S.; Hobza, P. *J. Am. Chem. Soc.* **2002**, *124*, 3366.

(13) Beijer, F. H.; Sijbesma, R. P.; Kooijman, H.; Spek, A. L.; Meijer, E. W. *J. Am. Chem. Soc.* **1998**, *120*, 6761.

(14) Söntjens, S. H. M.; Sijbesma, R. P.; van Genderen, M. H. P.; Meijer, E. W. *J. Am. Chem. Soc.* **2000**, *122*, 7487, specifically p 7493.

Table 1. Interaction Energies (kcal/mol), Obtained at the B3LYP/6-311+G(d,p)//B3LYP/6-31G(d,p) Level of Theory in Vacuo and “in CHCl₃” (Mimicked by IEFPCM; in Parentheses)

description (reaction)	keto/keto	enol/enol	keto/enol
4 monomers → 2 dimers (A)	-83.52 (-34.39)	-55.30 (-24.44)	-69.41 (-29.42)
2 dimers → stacked dimer (B)	-1.65 (3.50)	-0.29 (2.86)	-1.01 (3.74)
4 monomers → stacked dimer (C)	-85.18 (-30.89)	-55.59 (-21.58)	-70.42 (-25.68)
4 monomers → 2 monomer stacks (D)	7.85 (10.79)	4.02 (7.27)	0.36 (5.35)
2 monomer stacks → stacked dimer (E)	-93.02 (-41.68)	-59.61 (-28.85)	-70.79 (-31.03)

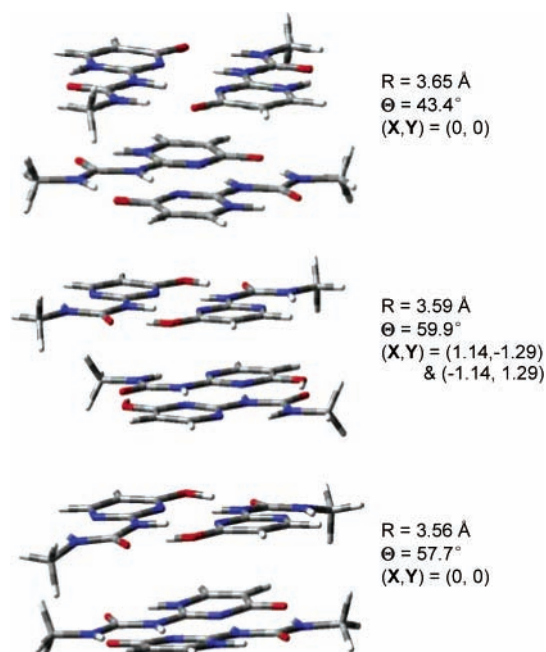


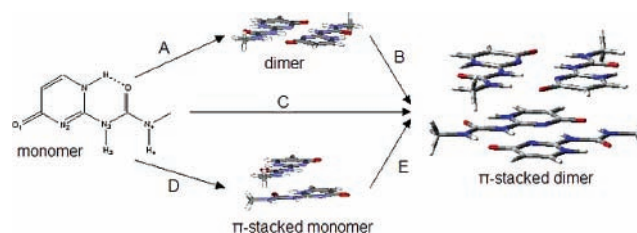
Figure 3. Optimized structures of π -stacked keto dimers (**1k-1k/1k-1k**; top), π -stacked enol dimers (**1e-1e/1e-1e**; bottom left), and hetero- π -stacked keto and enol dimers (**1k-1k/1e-1e**; bottom right), together with the optimized values of R , Θ , and (X,Y) .

To evaluate the interaction energies in this system, the reaction enthalpies for dimerization (reaction A), π -stacking of dimers (reaction B), π -stacking of monomers in the relative orientation they have in the optimized stacked dimer (reaction D), and dimerization of these π -stacked monomers (reaction E) were calculated as depicted in Scheme 1 for **1k**; the cases for **1e** and the heterostack of **1k** and **1e** are analogous. The resulting enthalpies are given in Table 1 both for these reactions in vacuo, and in a dielectric medium mimicking chloroform, using the IEF-PCM model.¹⁵ From the data in Table 1 it follows that, in the gas-phase, dimer formation is attractive both with and without π -stacking

(15) (a) Cancès, M. T.; Mennucci, B.; Tomasi, J. *J. Chem. Phys.* **1997**, *107*, 3032. (b) Cossi, M.; Barone, V.; Mennucci, B.; Tomasi, J. *Chem. Phys. Lett.* **1998**, *286*, 253.

(reactions A and C), but the latter has a more negative enthalpy in all cases. In other words, the π -stacking of the H-bonded dimers (path B) is enthalpically attractive. However, this is not the case for the π -stacking of the not yet H-bonded monomers. The enthalpy for π -stacking of **1k/1k** and of **1e/1e** is about +4 (7.85/2) and 2 kcal/mol, respectively. In solution, π -stacking of H-bonded dimers is slightly less attractive (all reaction enthalpies slightly >0 with B3LYP, but just less than zero with several other functionals (MPW1B95 and B98; see Supporting Information)), but π -stacking of the monomers is now even more strongly uphill.

Scheme 1. Stepwise Construction of π -Stacked Dimers from Monomers for Homostack of **1k**



These positive values for π -stacking of the monomers are likely caused by the repulsive electrostatic interactions of the monomer dipoles that have a partially parallel orientation, as has also been found for stacking of the DNA monomers.¹⁶ For **1k** and **1e**, these monomer dipoles are calculated to be 7.3 and 3.6 D, respectively, while for the π -stacked monomers *in the geometry they have in the optimized stacked dimer*, these values are 13.1 and 6.0 D, respectively. The π -stacking of monomers thus is energetically uphill and will likely not occur at all in competition with multiple H-bond formation (optimization of a wide variety of starting geometries for two π -stacked monomers resulted in the H-bonded dimer **1k-1k**). If monomer stacking can nevertheless be

(16) (a) Hill, G.; Forde, G.; Hill, N.; Lester, W. A., Jr.; Sokalski, W. A.; Leszczynski, J. *Chem. Phys. Lett.* **2003**, *381*, 729. (b) See for a discussion of correlation effects: Jurecka, P.; Hobza, P. *J. Am. Chem. Soc.* **2003**, *125*, 15608.

accomplished, then it strengthens the H-bonding. This is obvious from reaction E, which yields the most negative values in all three cases, both in vacuo and in solution. Therefore, if monomer stacking is favored by introduction of a covalent linker between the hydrogen bonding moieties such as in refs 9b and 10, the formation of hydrogen bonds is a cooperative process. A similar situation is found in DNA, in which monomer stacking prior to hydrogen-bond formation is achieved via the covalent linkage of the bases to the phosphodiester backbone.

It is important to note that these findings are independent of the precise theoretical method. Using TRIM local MP2¹⁷ computations that recover ~99.7% of the untruncated MP2 correlation energy [LMP2/6-311G(d,p)],¹⁸ and which thus use a very different methodology to account for the correlation of electrons than the B3LYP method used above, nearly identical structures were obtained as with B3LYP. Only one significant difference was observed, which relates to the π -stacking distance R . Using LMP2, R was computed to be 3.15 Å in **1k-1k/1k-1k**, which deviates significantly from the experimentally observed value of 3.55 Å that is reproduced accurately with B3LYP (vide supra). In addition, the stacking energy (reaction B) itself is computed with LMP2 to be rather high (19 kcal/mol) for the stacked dimer, which again is not in line with experiment (no precise values known, but estimated to be clearly <10 kcal/mol).^{10,13} Analogously, we performed single-point computations using the MPW1B95 and B98 functionals, which were very recently evaluated to give high-accuracy data on noncovalently bound complexes.¹⁹ These functionals predict π -stacking to be slightly more favorable than B3LYP does, but otherwise all observations are similar. Specifically, all π -stacking of monomers in solution is computed to be enthalpically uphill (see Supporting Information). Therefore, we discuss the generalization of our findings on the basis of the B3LYP data, but note that the strengthening of hydrogen bonding upon π -stacking and the proposed explanations thereof would also follow from the LMP2, MPW1B95, and B98 data.

As noted, the π -stacking itself influences the H-bonds. Such effects could, in principle, be expected, given the significance of orbital interactions in multiply H-bonded systems, as shown, e.g., for DNA and related H-bonded dimers.^{7a} In addition, similar effects of π -stacking have been computed for the H-bond strength in a model system of substituted pyridines π -stacked with a benzene ring.²⁰ From an NBO analysis of the systems presently under study, the largest interactions between the H-bonded components arise from charge transfer from the heteroatom lone pair(s) to the

corresponding N–H antibonding orbital [e.g., LP¹ on (O1) \rightarrow $\sigma^*(\text{N1-H1})$]. Since the dimers are composed of self-complementary components, in this case no net charge transfer from one monomer to the other occurs, but this secondary interaction energy does contribute to the interaction energy to a large extent (up to 40 kcal/mol in dimer **1k-1k**). Interestingly, this value increases upon π -stacking, as depicted in Figure 4, which is linked to a decreased NBO

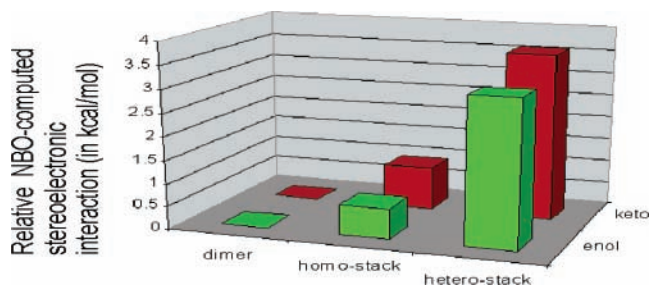


Figure 4. Effect (in kcal/mol) of π -stacking on the NBO-computed interaction energy between H-bond components.

energy gap and slightly increased Fock matrixes between the electron-donating LPs and $\sigma^*(\text{N1-H1})$ upon stacking. The increased interaction is clear but modest in the homo-stacked cases of **1k-1k/1k-1k** and **1e-1e/1e-1e**, but in the case of heterostacks such as **1k-1k/1e-1e** it amounts to ~3 kcal/mol for each component. This strengthened interaction also clarifies the hitherto puzzling observation of a significantly larger occurrence of keto–enol stacks than could be expected on the basis of the individual free energies of dimerization.^{9b,10} As an overall result, π -stacking itself increases the H-bonding in multiply H-bonded systems. The effect of stacking on hydrogen bonding is a secondary effect, with obvious analogies to the secondary effects between neighboring hydrogen bonds within a single dimer.^{8a}

In summary, from hybrid DFT and local MP2 calculations it follows that π -stacking strengthens the hydrogen bonds in multiply H-bonded dimers. This is attributed to the enthalpy increase upon π -stacking of the monomers and to the increased charge-transfer interactions between the H-bonding partners. These findings are not dependent on the particular nature of the H-bonding components or the particular theoretical model used (DFT or local MP2). As a result, it is to be expected that the increase of the hydrogen bonding strength upon π -stacking is quite general and thus, e.g., plays a role in the geometry and hybridization of DNA.

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Supporting Information Available: Crystallographic data of **1k-1k** and **1e-1e** for validation purposes, plots such as Figure 2 for **1e-1e/1e-1e**, and **1k-1k/1e-1e**, and MPW1B95 and B98 data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(17) Lee, M. S.; Maslen, P. E.; Head-Gordon, M. *J. Chem. Phys.* **2000**, *112*, 3592.

(18) Kong, J.; White, C. A.; Krylov, A. I.; Sherrill, C. D.; Adamson, R. D.; Furlani, T. R.; Lee, M. S.; Lee, A. M.; Gwaltney, S. R.; Adams, T. R.; Ochsenfeld, C.; Gilbert, A. T. B.; Kedziora, G. S.; Rassolov, V. A.; Maurice, D. R.; Nair, N.; Shao, Y.; Besley, N. A.; Maslen, P. E.; Dombroski, J. P.; Daschel, H.; Zhang, W.; Korambath, P. P.; Baker, J.; Byrd, E. F. C.; Van Voorhis, T.; Oumi, M.; Hirata, S.; Hsu, C.-P.; Ishikawa, N.; Florian, J.; Warshel, A.; Johnson, B. G.; Gill, P. M. W.; Head-Gordon, M.; Pople, J. A. *J. Comput. Chem.* **2000**, *21*, 1532.

(19) Zhao, Y.; Truhlar, D. G. *J. Phys. Chem. A* **2004**, *108*, 6908.

(20) Mignon, P.; Loverix, S.; De Proft, F.; Geerlings, P. *J. Phys. Chem. A* **2004**, *108*, 6038.