DOI: 10.1002/ejoc.200800294

Tautomeric Equilibria in 3-Amino-1-(2-aminoimidazol-4-yl)prop-1-ene, a Central Building Block of Marine Alkaloids

Yin Wei[a] and Hendrik Zipse*[a]

Keywords: 2-Aminoimidazole / Tautomeric equilibria / ab initio calculations

The tautomers **I**–**IV** of the marine metabolite 3-amino-1-(2-aminoimidazol-4-yl)prop-1-ene (**1**) were previously suggested to have rather similar stabilities.[1,2] Through a series of DFT and ab initio calculations, their relative stabilities were investigated in both the gas phase and in water, and also compared to their Z-isomers **V**–**VIII**. The tautomers **I** and **III** have almost identical stability in the gas phase and in water. The Z-isomer **VII** is more stable than other tautomers in the gas phase and quite competitive with **I** and **III** in water. The tautomers **II** and **IV** are much less stable and unlikely to coexist in equilibrium with **I** and **III**. The calculated pK_a of **1**-H$^+$ of +10.9 suggests that **1** is fully protonated even under mildly acidic conditions. Protonation decreases the stability difference between the most stable tautomer **III** and the less stable tautomer **IV**.

Introduction

3-Amino-1-(2-aminoimidazol-4-yl)prop-1-ene (**1**) is a metabolite of the 2-aminoimidazole class holding a central position in the modular synthesis of a large variety of marine alkaloids.[1–6] The flexible use of this building block in the biosynthesis of pyrrole-imidazole alkaloids has recently been suggested to be due to the variable reactivity of **1**, acting as a nucleophile in tautomeric forms **I** and **III** and as electrophile in tautomeric forms **II** and **IV**. Equilibration between the respective tautomeric forms thus stands at the center of a comprehensive biosynthetic scheme proposed by Al-Mourabit et al.[1] In order to support the participation of different tautomeric forms of **1** along various biosynthetic pathways, Al-Mourabit et al. have recently described the results of theoretical studies suggesting the comparable stability of the four tautomeric forms **I**–**IV** of **1** shown in Figure 1.[2] In the light of known stability data for "aromatic" and "non-aromatic" tautomers of the imidazole parent system,[7–9] the high stability of tautomer **IV** certainly comes as a surprise. Using selected theoretical methods known for their performance in the prediction of thermodynamic stabilities,[10–12] we have therefore revisited the question of thermodynamic stability of tautomeric forms of **1**.

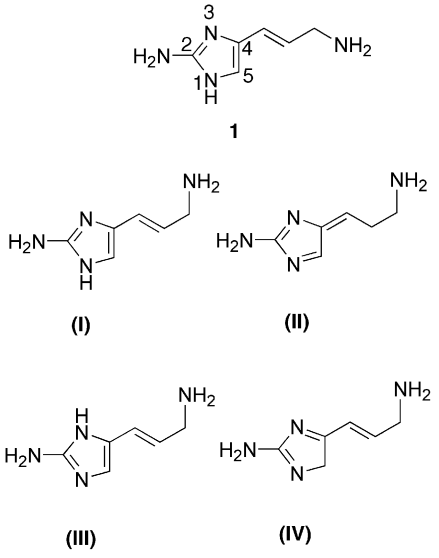

Figure 1. 2-Aminoimidazole metabolite **1** and its tautomers **I**–**IV**.

Results and Discussion

Stabilities of Neutral Tautomers

Initial studies were performed at the RHF/6-31G(d) level of theory, the same level used by Al-Mourabit et al. (Table 1).[2,13] The first entry of Table 1 is taken from Ref. 2 and shows tautomer **IV** to be more stable than the other tautomers by around 5 kJ/mol. Carefully searching the conformational space of all four systems by rotation around all rotatable bonds, we identified 18 conformers for tautomers

[a] Department Chemie und Biochemie, Ludwig-Maximilians-Universität München,
Butenandtstrasse 5–13, 81377 München, Germany
Fax: +49-89-218077738
E-mail: zipse@cup.uni-muenchen.de

Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.

I, **III**, and **IV**, and 9 conformers for **II**, respectively (see Supporting Information). According to this conformational analysis, the results reported in Ref. 2 are based on the best conformer for **IV**, but higher energy conformers of tautomers **I**–**III**. Using the best conformers for all four tautomers, the relative energies reported in the second row of Table 1 are obtained. Accordingly, tautomer **III** is the most stable one at the RHF/6-31G(d) level, the other forms being less stable by, at most, 6 kJ/mol. Including thermal corrections to enthalpies at 298.15 K (ΔH_{298} in Table 1) does not lead to any significant changes in relative energies. The relative enthalpies have subsequently been recalculated with three other theoretical methods known for their performance in predicting accurate thermochemical data. This includes calculations for all conformers with Becke's B98 hybrid functional[14,15] in combination with the 6-31G(d) basis set, the MP2(FC)/6-31+G(2d,p)//B98/6-31G(d) level recently identified as a reliable method for the calculation of proton and methyl cation affinities of N- and P-bases,[11] and the G3MP2B3 compound method developed by Curtiss et al.[15,16] The G3MP2B3 level is considered to be the most accurate in this series of methods.[16,17]

Table 1. Relative energies [kJ/mol] of the best conformer of tautomers **I**–**IV** in Figure 1.

	Level of theory	I	II	III	IV
ΔE_{tot}[a]	RHF/6-31G(d)	4.9	5.0	5.9	0.0
ΔE_{tot}[b]	RHF/6-31G(d)	0.5	6.0	0.0	1.7
ΔH_{298}	RHF/6-31G(d)	0.1	4.9	0.0	0.2
ΔH_{298}	B98/6-31G(d)	1.2	12.0	0.0	15.3
ΔH_{298}[c]	MP2/6-31+G(2d,p)//B98/6-31G(d)	1.4	27.5	0.0	32.9
ΔH_{298}	G3MP2B3	0.1	21.8	0.0	22.9

[a] Ref.[2] [b] This work. [c] Thermochemical corrections calculated at B98/6-31G(d) level.

All methods agree in that tautomers **I** and **III**, which include the aromatic imidazole ring system in its standard tautomeric form, are of almost identical stability, while tautomers **II** and **IV** are much less stable. At G3MP2B3 level tautomers **II** and **IV** are predicted to be less favorable than **III** by 21.8 kJ/mol and 22.9 kJ/mol, respectively. Thus, tautomers **II** and **IV** are unlikely to coexist with the other tautomers in the gas phase.[18]

The structures of the energetically most favorable conformers at the MP2(FC)/6-31+G(2d,p)//B98/6-31G(d) level of theory for **I**–**IV** are shown in Figure 2. All structures have in common that both amino groups are non-planar in all four tautomers, and that the side chain attached to the C4 position assumes an extended conformation.

Conditions favoring tautomeric equilibration between isomers **I**–**IV** will also allow for the *E*/*Z*-isomerization of the C–C double bond in **1**. While Z-configured alkenes are usually considered to be less stable than the corresponding *E*-isomers, other effects may compensate these differences in polyfunctional systems such as **1**. We have therefore also studied tautomers **V** – **VIII** (Figure 3) derived from **I**–**IV** through *E*/*Z* isomerization. Conformational searches performed at RHF/6-31G(d) and B98/6-31G(d) level again identified a large number of different conformers. The energetically most favorable conformer was subsequently used for comparison to isomer **III** (Table 2).

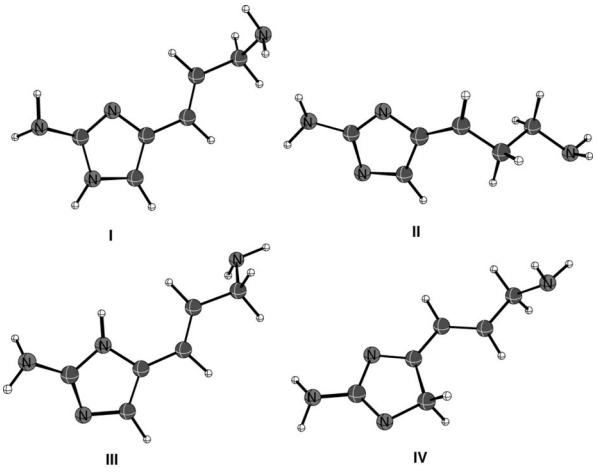

Figure 2. Structures of the best conformer of tautomers **I**–**IV** at the MP2(FC)/6-31+G(2d,p)//B98/6-31G(d) level of theory.

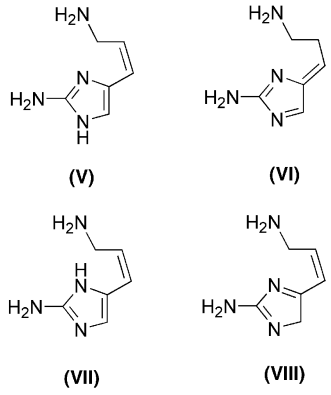

Figure 3. Z-Isomers of tautomers **I**–**IV**.

Table 2. Stabilities [kJ/mol] of the best conformer of tautomers **V**–**VIII** (Figure 3) relative to tautomer **III**.[a]

	Level of theory	V	VI	VII	VIII
ΔH_{298}	RHF/6-31G(d)	10.2	–3.0	–3.8	11.5
ΔH_{298}	B98/6-31G(d)	13.7	4.0	–17.7	22.5
ΔH_{298}	MP2/6-31+G(2d,p)//B98/6-31G(d)	3.7	19.6	–15.4	39.5
ΔH_{298}	G3MP2B3	2.5	14.6	–12.3	29.7

[a] Using the best conformer of **III** as the reference.

All methods agree that tautomer **VII** is more stable than **III**. Concentrating on the best (G3MP2B3) results, this stability difference amounts to –12.3 kJ/mol. Inspection of the structure of **VII** (Figure 4) identifies the formation of an intramolecular hydrogen bond between the terminal NH_2 group and the imidazole ring system as the cause for this enhanced stability. *E*/*Z*-isomerization of the other three tautomers **I**, **II**, and **IV** also leads to some changes in their relative stability, but the effects are smaller than observed

for **III**. In conclusion we can thus state that gas phase enthalpies predict isomer **VII** as the only significantly populated tautomeric/isomeric form of **1** under equilibrating conditions.

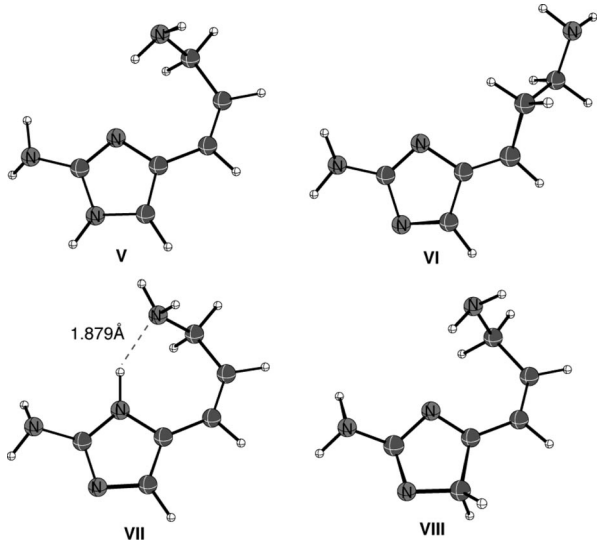

Figure 4. Structures of the best conformer of tautomers **V**–**VIII** at the MP2(FC)/6-31+G(2d,p)//B98/6-31G(d) level of theory.

In order to test the influence of aqueous solvation effects on this conclusion, we have calculated solvation free energies in water ΔG_{solv} for all conformers of tautomers **I**–**VIII** at the PCM/UAHF/RHF/6-31G(d) level[19,20] using the previously optimized gas phase structures. Combination of these solvation free energies with gas phase enthalpies obtained at either MP2(FC)/6-31+G(2d,p)//B98/6-31G(d) or G3MP2B3 level yields the relative enthalpies in water ΔH_{298} (water) compiled in Table 3 in columns 3 and 4. Structural relaxation in aqueous solution can, of course, lead to significant changes in relative stabilities. The solvation free energies ΔG_{solv} for all conformers of tautomers **I**–**VIII** were therefore calculated again at the PCM/UAHF/RHF/6-31G(d) level using the optimized structures in aqueous solution at PCM/UAHF/B98/6-31G(d) level.[21] In the same manner, combination of these solvation free energies with gas phase enthalpies obtained at either MP2(FC)/6-31+G(2d,p)//B98/6-31G(d) or G3MP2B3 level yields the relative enthalpies in water ΔH_{298} (water) compiled in Table 3 in columns 5 and 6. The numbers shown for isomers **I**–**VIII** are those for the most stable conformers in water.

Comparison of relative enthalpies in the gas phase ΔH_{298} (gas, G3MP2B3) and in aqueous solution ΔH_{298} (water, G3MP2B3) shows the most significant changes for the stability of isomer **VII**. From the results obtained at G3MP2B3 level with relaxed geometries in aqueous solution (column 6 in Table 3) it is evident that conformer **VII** is much less well solvated than all other tautomers, which, in essence, means that the benefit of the intramolecular hydrogen bond is lost in a strongly polar medium such as water. Z-isomer **VII** therefore ends up being less stable by 4.5 kJ/mol than E-isomer **III** under aqueous conditions. Surveying the results for all other systems in Table 3 we note that isomer **I** is predicted to be equally stable as **III**. Most importantly we also note that isomers void of the aromatic imidazole ring system (**II**, **IV**, **VI**, and **VIII**) are rather unstable also under aqueous conditions. Comparison of the results obtained at MP2 and G3MP2B3 level indicates that none of these conclusions depends on the particular choice of gas phase energies. Also, the influence of solution phase relaxation on the relative stability of tautomers **I**–**VIII** is rather minor.

Table 3. Relative energies [kJ/mol] of isomers **I**–**VIII** in the gas phase and in water.[a]

Isomer	G3MP2B3	MP2	G3MP2B3	MP2	G3MP2B3
	ΔH_{298}[b] (gas)	ΔH_{298}[c] (water)	ΔH_{298}[d] (water)	ΔH_{298}[e] (water)	ΔH_{298}[f] (water)
		gas phase geometries		solution phase geometries	
I	0.1	0.5	–0.1	0.4	–0.2
II	21.8	34.5	29.7	36.7	31.8
III	0.0	0.0	0.0	0.0	0.0
IV	22.9	25.4	15.2	28.3	19.9
V	2.5	10.8	10.2	10.0	9.5
VI	14.6	29.9	25.7	31.6	27.4
VII	–12.3	–1.7	2.8	0.7	4.5
VIII	29.7	40.0	29.9	42.1	32.1

[a] Using the best conformer of **III** as the reference. [b] The best conformer G3MP2B3 gas phase data. [c] Sum of H_{298}[gas phase, MP2/6-31G+(2d,p)//B98/6-31G(d)] and ΔG_{solv} calculated at PCM/UAHF/RHF/6-31G(d)//B98/6-31G(d) level. [d] Sum of H_{298}(gas phase, G3MP2B3) and ΔG_{solv} calculated at PCM/UAHF/HF/6-31G(d)//B98/6-31G(d) level. [e] Sum of H_{298}[gas phase, MP2/6-31G+(2d,p)//B98/6-31G(d)] and ΔG_{solv} calculated at PCM/UAHF/RHF/6-31G(d)//PCM/UAHF/B98/6-31G(d) level. [f] Sum of H_{298}(gas phase, G3MP2B3) and ΔG_{solv} calculated at PCM/UAHF/HF/6-31G(d)//PCM/UAHF/B98/6-31G(d) level.

Stabilities of Protonated Forms

The low thermodynamic stability of tautomeric forms **II** and **VI** casts some doubt on their proposed involvement as electrophiles in synthetic and biosynthetic reactions.[1,2] Especially under acidic conditions it would seem conceivable that the protonated forms of **1** are much more likely to act as electrophiles. The actual availability of the cationic forms depend, of course, on the basicity of **1** in aqueous solution and we use the thermodynamic cycle shown in Figure 5 to derive a quantitative estimate for the pK_a of the protonated form of **1** in aqueous solution under standard conditions. The basicity of **1** is compared here to that of 2-aminoimidazole **2**, whose protonated form is known to have pK_a = +8.5.[28] The reaction free energy in the gas phase $\Delta G_{rxn,gas}$ can accurately be calculated using the same methods as before and a value of –16.4 kJ/mol is obtained at G3MP2B3 level. Additional consideration of solvation effects at the PCM/UAHF/RHF/6-31G(d)//PCM/UAHF/B98/6-31G(d) level leads to a reaction free energy in solution $\Delta G_{rxn,sol}$ of –13.8 kJ/mol (see the detailed calculation procedure in Supporting Information). This implies that metabolite **1** is more basic than 2-aminoimidazole **2** by 2.4

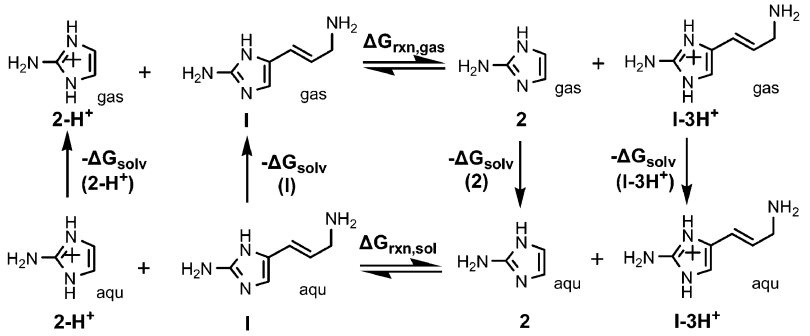

Figure 5. The thermodynamic cycle used to calculate relative pK_a in aqueous solution.

pK_a units with pK_a(**1**-H$^+$) = +10.9. Under the, in part, strongly acidic reaction conditions employed in transformations of **1** and its derivatives involving either mineral acids or CH_3SO_3H (pK_a = –0.6 in aqueous solution)[2,27] we can thus assume that **1** is present quantitatively in its protonated form. The reactivity of **1** under these conditions will thus be that of **I**-3H$^+$ or one of its tautomeric forms. In order to explore the possibility that the energetically unfavorable neutral tautomers **II** and **IV** are stabilized at the protonated stage we have used the same theoretical methods as before to compare the relative stabilities of the three tautomers shown in Figure 6. The relative energies of these systems are compiled in Table 4. As expected the tautomer **I**-3H$^+$ is the most stable one. The tautomer **IV**-1H$^+$ is less stable than **I**-3H$^+$ by 7.6 kJ/mol in aqueous solution, which represents a much smaller energy difference of these tautomers as compared to the neutral stage (19.9 kJ/mol). A second tautomer **IV**-3H$^+$ is much less stable than **IV**-1H$^+$ and therefore most likely not involved in reactions under acidic conditions.

Table 4. Relative energies [kJ/mol] of cationic tautomers in the gas phase and in water.[a]

Isomer	G3MP2B3 ΔH_{298}[b] (gas)	MP2 ΔH_{298}[c] (water)	G3MP2B3 ΔH_{298}[d] (water)	MP2 ΔH_{298}[e] (water)	G3MP2B3 ΔH_{298}[f] (water)
		gas phase geometries		solution phase geometries	
I-3H$^+$	0.0	0.0	0.0	0.0	0.0
IV-1H$^+$	13.4	12.8	8.7	12.4	7.6
IV-3H$^+$	68.2	63.5	57.4	61.4	55.4

[a] Using the best conformer of **I**-3H$^+$ as the reference. [b] The best conformer G3MP2B3 gas phase data. [c] Sum of H_{298}[gas phase, MP2/6-31G+(2d,p)//B98/6-31G(d)] and ΔG_{solv} calculated at PCM/UAHF/RHF/6-31G(d)//B98/6-31G(d) level. [d] Sum of H_{298}(gas phase, G3MP2B3) and ΔG_{solv} calculated at PCM/UAHF/HF/6-31G(d)//B98/6-31G(d) level. [e] Sum of H_{298}[gas phase, MP2/6-31G+(2d,p)//B98/6-31G(d)] and ΔG_{solv} calculated at PCM/UAHF/RHF/6-31G(d)//PCM/UAHF/B98/6-31G(d) level. [f] Sum of H_{298}(gas phase, G3MP2B3) and ΔG_{solv} calculated at PCM/UAHF/HF/6-31G(d)//PCM/UAHF/B98/6-31G(d) level.

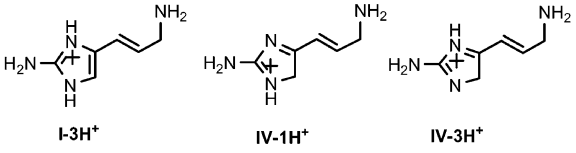

Figure 6. Tautomeric forms of protonated metabolite **1**.

One example where occurrence of the unstable neutral tautomer **IV** has been suggested concerns the H/D exchange reactions in compound **3** in refluxing deuterated trifluoroacetic acid (Figure 7).[2] If we assume the basicity of **3** to parallel that of **1** then **3** will be fully protonated under these conditions. Selective H/D exchange at position C5 as well as *cis*/*trans* isomerization to yield product **4** without H/D exchange at C7 can be rationalized with the three protonated forms **5**, **6** and **7**. As already implied by Al-Mourabit et al. H/D exchange at all heteroatoms can be expected to be fast under these conditions as compared to *cis*/*trans* isomerization. This latter process can be initiated through formation of C5-protonated tautomer **5** and subsequent cyclization to intermediate **6**. Ring-opening to intermediate **7** and isomerization between the C5- and N1-protonated forms complete the reaction sequence. Other processes, in which neutral **1** has been suggested to act as electrophile,[1] may similarly involve the protonated form of **1** instead.

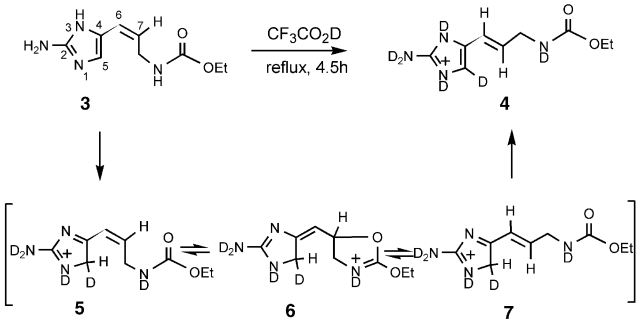

Figure 7. H/D-Exchange and *cis*/*trans* isomerization of **3** under acidic conditions as reported in ref.[2]

Conclusions

In conclusion, the tautomers **II** and **IV** of 2-aminoimidazole metabolite **1** reported as energetically favorable before[2] are unlikely to coexist with tautomers **I** and **III**, in the gas phase as well as in water. The tautomers **I** and **III** have almost identical stability in the gas phase and in water, and thus will both be accessible in solution. The Z-isomer of **III**, tautomer **VII**, should not be ignored because it is more stable than any other tautomer in the gas phase and competitive with **I** and **III** in water. These conclusions are independent of the particular theoretical methods chosen for solution phase calculations. The low thermodynamic stability of tautomers **II** and **IV** casts some doubt on the role of these isomers as electrophiles in synthetic and biosynthetic reactions.[1] The protonated form of the 2-aminoimidazole moiety, which is present in many synthetically used derivatives of **1**, may fill this role much more comfortably and with much less thermodynamic effort.[3–6] The calculated pK_a of **1**-H$^+$ of +10.9 in aqueous solution indeed suggests that **1** is present quantitatively in its protonated form even under mildly acidic reaction conditions. Protonation also decreases the stability difference between the most stable tautomer **III** and the less stable tautomer **IV**, offering an explanation for the apparent involvement of this latter tautomer in H/D exchange experiments.

Computational Details

Geometry optimizations of all systems have been performed at the RHF/6-31G(d) and the B98/6-31G(d)[14,15] level of theory. Thermochemical corrections to enthalpies at 298.15 K have been calculated at the same level of theory using the rigid rotor/harmonic oscillator model. Single point calculations at MP2(FC)/6-31+G(2d,p) level have been calculated based on the B98/6-31G(d) geometries. Combination of these energies with thermochemical corrections obtained at B98/6-31G(d) level yield enthalpies described as "H_{298}[MP2(FC)/6-31+G(2d,p)//B98/6-31G(d)]" in the text. For the four best conformers obtained at MP2(FC)/6-31+G(2d,p)//B98/6-31G(d) level refined relative enthalpies have been calculated using the G3(MP2)B3 compound method developed by Curtiss et al.[15–17] For the sake of consistency identical B98/6-31G(d) geometries were used in the MP2(FC)/6-31+G(2d,p) and G3(MP2)B3 calculations. Solvent effects have been calculated using the PCM continuum solvation model in its IEF-PCM incarnation[20,22–24] in combination with UAHF radii.[19] All calculations have been performed with Gaussian 03, Revision D.01.[25]

Supporting Information (see also the footnote on the first page of this article): Energies for all conformers of all isomers at different levels of theories.

Acknowledgments

This study was supported by the Deutsche Forschungsgemeinschaft (DFG) in the focus program "Organocatalysis" under Grant DFG Zi 426/10–1.

[1] A. Al-Mourabit, P. Potier, *Eur. J. Org. Chem.* **2001**, 237–243.
[2] R. Abou-Jneid, S. Ghoulami, M.-T. Martin, E. T. H. Dau, N. Travert, A. Al-Mourabit, *Org. Lett.* **2004**, *6*, 3933–3936.
[3] H. Hoffmann, T. Lindel, *Synthesis* **2003**, 1753–1783.
[4] P. S. Baran, D. P. O'Malley, A. L. Zografos, *Angew. Chem. Int. Ed.* **2004**, *43*, 2674–2677.
[5] D. E. N. Jacquot, T. Lindel, *Curr. Org. Chem.* **2005**, *9*, 1551–1565.
[6] M. Köck, A. Grube, I. B. Seiple, P. S. Baran, *Angew. Chem. Int. Ed.* **2007**, *46*, 6586–6594.
[7] a) G. Rauhut, *Adv. Heterocycl. Chem.* **2001**, *81*, 1–53; b) V. I. Minkin, A. D. Garnovskii, J. Elguero, A. R. Katritzky, O. V. Denisov, *Adv. Heterocycl. Chem.* **2000**, *76*, 157–323.
[8] P. I. Nagy, F. R. Tejada, W. S. Messer Jr, *J. Phys. Chem. B* **2005**, *42*, 22588–22602.
[9] I. Alkorta, J. Elguero, J. F. Liebman, *Strut. Chem.* **2006**, *17*, 439–444.
[10] Y. Wei, I. Held, H. Zipse, *Org. Biomol. Chem.* **2006**, *4*, 4223–4230.
[11] Y. Wei, T. Singer, H. Mayr, G. N. Sastry, H. Zipse, *J. Comput. Chem.* **2008**, *29*, 291–297.
[12] Y. Wei, G. N. Sastry, H. Zipse, *J. Am. Chem. Soc.* **2008**, *130*, 3473–3477.
[13] We assume that Al-Mourabit et al. used the RHF/6-31G(d) level of theory in their calculations. The level of theory was described by the acronym "6-316*" in ref. 2 (typo?), most probably the basis set "6-31G*" is meant.
[14] H. L. Schmider, A. D. Becke, *J. Chem. Phys.* **1998**, *108*, 9624–9631.
[15] L. A. Curtiss, P. C. Redfern, K. Raghavachari, *J. Chem. Phys.* **2005**, *123*, 124107–124118.
[16] P. C. Baboul, L. A. Curtiss, P. C. Redfern, K. Raghavachari, *J. Chem. Phys.* **1999**, *110*, 7650–7657.
[17] S. W. Paine, A. J. Kresge, A. Salam, *J. Phys. Chem. A* **2005**, *109*, 4149–4153.
[18] The non-aromatic C2-H tautomer of **1** is ruled out here because it is much less stable than all other tautomers. Preliminary calculations at B98/6-31G(d) level indicate relative energies between **III** and the C2-H tautomer in excess of 90 kJ/mol, much in line with previous studies of non-aromatic tautomers.[7–9]
[19] a) C. Amovilli, V. Barone, R. Cammi, E. Cances, M. Cossi, B. Mennucci, C. S. Pomelli, J. Tomasi, *Adv. Quantum Chem.* **1998**, *32*, 227–261; b) M. Cossi, G. Scalmani, N. Rega, V. Barone, *J. Chem. Phys.* **2002**, *117*, 43–54.
[20] M. T. Cancès, B. Mennucci, J. Tomasi, *J. Chem. Phys.* **1997**, *107*, 3032–3041.
[21] The solvation free energies ΔG_{solv} were calculated at PCM/UAHF/RHF/6-31G(d) level because the PCM/UAHF model was parameterized at Hartree–Fock level. The solvation free energies ΔG_{solv} were also calculated at PCM/UAHF/B98/6-31G(d) level with optimized B98/6-31G(d) gas-phase geometries and solution-phase geometries, respectively, and combined with either MP2(FC)/6-31+G(2d,p)//B98/6-31G(d) or G3MP2B3 level to yield the relative enthalpies in water ΔH_{298}(water) (compiled in Table S-2, see Supporting Information). The resulting relative stabilities of tautomers **I**–**VIII** are essentially identical to those reported in Table 3.
[22] B. Mennucci, J. Tomasi, *J. Chem. Phys.* **1997**, *106*, 5151–5158.
[23] M. Cossi, V. Barone, B. Mennucci, J. Tomasi, *Chem. Phys. Lett.* **1998**, *286*, 253–260.
[24] M. Cossi, G. Scalmani, N. Rega, V. Barone, *J. Chem. Phys.* **2002**, *117*, 43–54.
[25] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery Jr, T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A.

Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J. A. Pople, *Gaussian 03*, revision D.01, Gaussian, Inc., Wallingford, CT, **2004**.

[26] V. I. Minkin, A. D. Garnovskii, J. Elguero, A. R. Katritzky, O. V. Denisko, *Adv. Heterocycl. Chem.* **2000**, *76*, 157–296.

[27] S. Brownstein, A. E. Stillman, *J. Phys. Chem.* **1959**, *63*, 2061–2062.

[28] C. R. Ganellin, in *Molecular and Quantum Pharmacology, Proceedings of the 7th Jerusalem Symposium on Quantum and Biochemistry*, D. Reidel Publishing Co., Dordrecht/Boston, **1974**, 43–55.

Received: March 19, 2008

