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On the tautomerism of maleimide and phthalimide derivatives☆

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Abstract

The tautomerism of maleimide and phthalimide and their derivatives was examined by means of *ab initio* MO theory. The molecular geometry of the various tautomers was completely optimized employing the 6-31G* basis set and the semiempirical AM1 method, respectively. Correlation energy effects were estimated using the MP2 formalism. The solvent influence on the tautomeric equilibria was considered by means of the quantum chemical PCM formalism within the ab initio MO theory and the Cramer–Truhlar method (C.J. Cramer and D.G. Truhlar, J. Am. Chem. Soc., 113 (1991) 8305) incorporated into the semiempirical AM1 calculations.

The results indicate the diketo tautomers of maleimide and phthalimide as the most stable ones both in the gas phase and in solution. The stepwise replacement of the oxygen atoms by nitrogen causes significant changes. Whereas the lactam–lactim tautomerism can still be neglected in all compounds, the amino–imino tautomerism gains considerable importance, in particular in the maleic and phthalic imidine systems, where the amino–imino forms are of comparable stability with the diimino forms.

1. Introduction

Cyclic imides are of great importance in synthetic organic chemistry, but are also fundamental compounds in biological systems. In particular, the cyclic imides of maleic and phthalic acid are of special interest. The five-membered ring of these compounds may be considered as a model for a cyclic peptide linkage. Based on IR and electron diffraction studies the planar diketo structure **1a** is generally accepted for maleimide [1–6]. This is supported by the results of semiempirical and ab initio MO theory [6–8]. There is a scarcity of studies considering the possibility of tautomerism for these molecules [9]. The absolute predominance of the diketo tautomer **1a** seems to be well-established for maleimide and phthalimide, although quantitative estimations of the proportions of the other tautomeric forms are missing. The situation changes considerably if the oxygen atoms are replaced by nitrogen atoms coming to the compounds maleic imidine and phthalic imidine. Whereas the inspection of UV spectra [10] suggests the diimino forms **6b/c** as preferred tautomers for phthalic imidine in analogy to the diketo form of maleimide, a detailed NMR study is in favour of the amino–imino tautomer **5a** in DMSO and D_2O solution [11]. Obviously, the

☆ Dedicated to Professor J. Tomasi on occasion of his 60th birthday.

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energy differences between the various tautomers seem to be by far smaller in the imidine series than for the parent compounds.

It is the aim of this paper to describe the structure and tautomerism in the maleic and phthalic imide and imidine series by means of quantum chemical methods in order to clarify the partially contradictory results. Based on the general experience that tautomeric equilibria of this type are strongly influenced by solvents, various theoretical models were tested for the estimation of the solvation contribution.

2. Details of calculations

The theoretical description of tautomerism is a very delicate problem. Numerous studies demonstrate serious shortcomings of the most semiempirical methods [12–20]. Only the AM1 method seems to be successful in a greater number of cases [20–24]. The application of ab initio MO theory indicates at least qualitatively correct results when using split-valence basis sets [17,19,25–28]. Inclusion of polarization functions is generally recommended, sometimes even the consideration of correlation energy seems to be necessary [17,19,25,26]. In our calculations, the geometries of all tautomers were completely optimized employing the 6-31G* basis set [29]. For the maleic acid derivatives, the influence of the correlation energy was estimated by means of the MP2 formalism [29]. Numerous experimental studies show a strong influence of solvents on the tautomeric equilibria. In order to describe the solvent effects, we used several quantum chemical reaction-field models. In the Polarizable Continuum Model (PCM), the contribution of the electrostatic solute–solvent interaction is calculated based on a very precise determination of the size and shape of a solute cavity in the solvent [30–33]. The solute cavity is composed of interlocking spheres centered at the atoms of the solute. The radii necessary for the construction of the spheres are related to the Mullikan charges of the atoms as suggested in Ref. [34]. For comparison, a solvation model recently proposed by Cramer and Truhlar [35–37] was tested. In the present version, this Hamiltonian model is connected with the semiempirical MNDO, AM1 and PM3 methods, whereas the PCM formalism is incorporated into ab initio program packages. In our calculations, the Cramer–Truhlar (CT) model was applied at the AM1 level. Water was selected as solvent in all cases. The GAUSSIAN 90 program package was used for the geometry optimizations [38]. The PCM and the CT formalism are parts of the HONDO 7 [39] and the SPARTAN program systems [40], respectively.

Table 1
Energy differences between the tautomers of maleimide and phthalimide in the gas phase and in solution in kJ mol^{-1}

Tautomer	6-31G*			AM1	
	ΔE_g	ΔE_g (MP2)	ΔG_s^a	$\Delta\Delta H_f^\circ$	$\Delta\Delta H_{f,s}^{\circ\,b}$
Maleimide					
1a	0.0[c]	0.0[d]	0.0	0.0	0.0
1b	98.7	94.5	86.9	99.8	93.4
1c	130.4	124.0	95.9	121.3	112.5
Phthalimide					
4a	0.0[e]		0.0	0.0	0.0
4b	99.2		87.4	99.8	92.0
4c	132.2		97.6	120.3	108.4

[a] PCM formalism.
[b] CT model.
[c] E_g (6-31G*//6-31G*) = −357.40763 a.u.
[d] E_g (MP2/6-31G*//6-31G*) = −358.40248 a.u.
[e] E_g (6-31G*//6-31G*) = −510.08091 a.u.

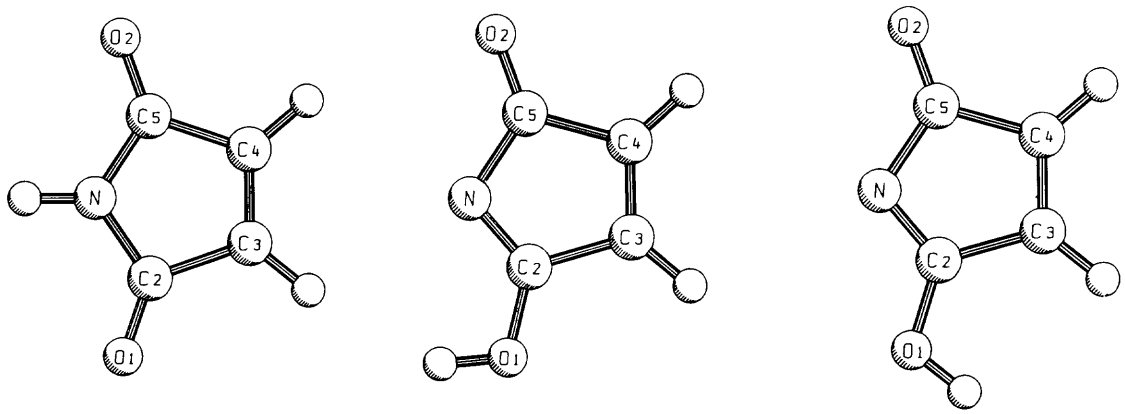

Fig. 1. The various tautomers of maleimide **1** (the corresponding tautomers of phthalimide **4** have an additional benzene ring annelated at the C_3-C_4 bond).

3. Results and discussion

Table 1 lists the 6-31G* and the AM1 energies of the maleimide and the phthalimide tautomers (Fig. 1) related to the most stable structure. Both the ab initio 6-31G* and the semiempirical AM1 results show a distinct predominance of the diketo forms **1a** and **4a** in agreement with the experimental data. The hydroxy-keto forms **1b,c** and **4b,c** are considerably less stable than the diketo tautomers both in the gas phase and in solution. The influence of the electron correlation on the stability order is negligible.

In Table 2, the optimized geometry parameters of maleimide determined by ab initio MO theory considering correlation energy and by the semiempirical AM1 method are compared with the electron diffraction results [6]. The agreement between theoretical and experimental data is satisfactory.

It may be interesting to describe the changes of the tautomeric equilibria for maleimide and phthalimide, if the two oxygen atoms are stepwise

Table 2
Comparison of ab initio and AM1 optimized geometry parameters of maleimide **1a** with electron diffraction data

Geometry Parameters[a]	6-31G*	MP2/6-31G*	AM1	Experimental[b]
N–C	1.381	1.394	1.416	1.409
C–C	1.502	1.497	1.516	1.508
C=C	1.319	1.341	1.349	1.344
C=O	1.185	1.220	1.231	1.206
C–H	1.071	1.083	1.090	1.096
N–H	0.996	1.013	0.987	1.025
∠ C–N–C	112.0	112.0	109.8	112.0
∠ N–C–C	105.1	105.1	106.5	106.8
∠N–C=O	126.7	126.5	125.2	123.9
∠ C–C–H	121.9	122.1	120.8	114.7

[a] Bond lengths in Å, bond angles in degrees.
[b] Ref. [6].

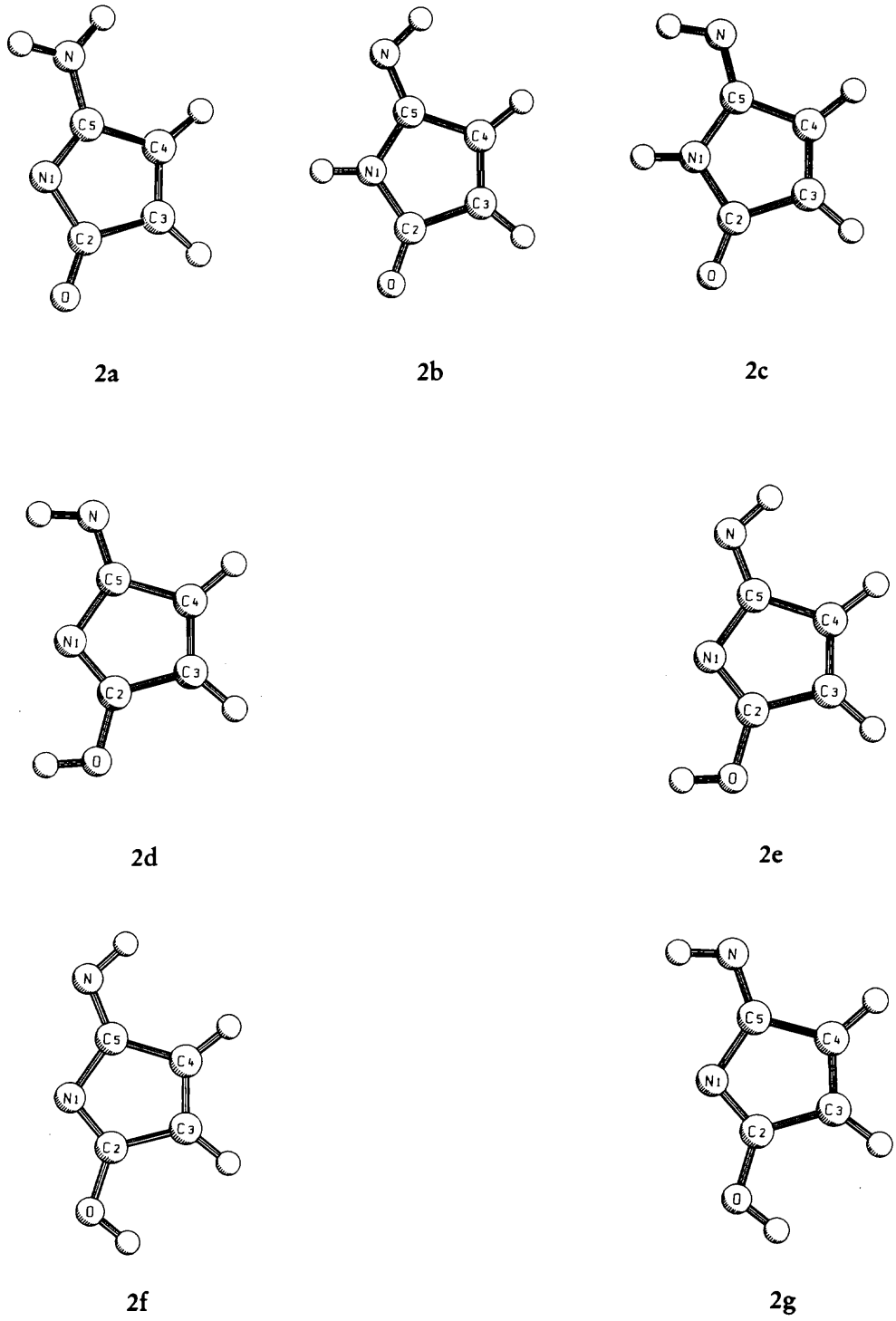

Fig. 2. The various tautomers of 1*H*-pyrrol-2-on-5-imine **2** (the corresponding tautomers of 3-iminoisoindolinone **5** have an additional benzene ring annelated at the C_3-C_4 bond).

Table 3
Energy differences between the tautomers of 1*H*-pyrrol-2-on-5-imine and 3-iminoisoindolinone in the gas phase and in solution kJ mol^{-1}

Tautomer	6-31G*			AM1	
	ΔE_g	ΔE_g (MP2)	ΔG_s^a	$\Delta\Delta H_f^\circ$	$\Delta\Delta H_{f,s}^{\circ\,b}$
1H-Pyrrol-2-on-5-imine					
2a	32.8	33.3	16.5	48.6	27.4
2b	0.0[c]	0.0[d]	0.0	11.6	11.5
2c	1.6	1.8	4.5	0.0	0.0
2d	72.8	68.2	79.1	71.8	66.8
2e	92.1	84.6	83.5	94.3	89.6
2f	123.7	114.0	88.3	115.1	108.2
2g	100.8	94.2	–[e]	90.7	82.6
3-Iminoisoindolinone					
5a	31.1		12.9	45.2	26.4
5b	0.0[f]		0.0	10.3	10.4
5c	0.4		3.9	0.0	0.0
5d	74.0		82.4	73.3	67.1
5e	93.9		82.0	94.5	87.7
5f	127.3		91.1	114.2	107.0
5g	103.4		91.3	91.0	83.4

[a] PCM formalism.
[b] CT model.
[c] E_g (6-31G*//6-31G*) = −337.55679 a.u.
[d] E_g (MP2/6-31G*//6-31G*) = −338.54018 a.u.
[e] No convergence.
[f] E_g (6-31G*//6-31G*) = −490.22783 a.u.

replaced by nitrogen atoms. Table 3 lists the results for the corresponding compounds 1*H*-pyrrol-2-one-5-imine **2** and 3-iminoisoindolinone **5** (Fig. 2) which were obtained after replacement of one oxygen atom in **1** and **4**. These molecules show the possibility of lactam–lactim and amino–imino tautomerism, respectively. As expected from the results for the parent compounds, the lactam–lactim tautomerism does not play a significant role. In the gas phase, the imino–keto tautomers **2b,c** and **5b,c** are the most stable forms. All hydroxy-imino forms **2d–g** and **5d–g**, respectively, are remarkably less stable. Contrary to this, the amino–imino tautomerism has a greater chance to be realized. The relative energy difference between the amino–keto and the imino–keto tautomers is considerably smaller than for the lactam–lactim equilibrium. The effect of correlation energy is insignificant. In solution the stability order of the tautomers is the same as in the gas phase both for ab initio MO theory and the AM1 method. However, the solvation stabilizes the amino–keto tautomers **2a** and **5a** more than the imino–keto tautomers **2b,c** and **5b,c**, respectively, although the latter still predominate. This is in good agreement with various experimental data for 3-iminoisoindolinone [10,41–44]. An IR study shows the absolute predominance of the imino–keto form independent of the substituents at the nitrogen atoms [41]. Based on NMR investigations the percentage of the imino–keto tautomer was estimated to be about 70% in DMSO [44].

Regarding the orientation of the hydrogen atom in the imino group, there is the possibility of *E*/*Z* isomerism. The quality of the quantum chemical methods to reproduce the correct arrangement may be evaluated by comparison with the NMR results on the 3-iminoisoindolinone, where the position of the imino proton was found in the *E*

configuration **5b** with an energy difference to the Z configuration **5c** of 3.6 kJ mol^{-1} in solution [44]. Ab initio MO theory provides a very small energy difference between the E and Z isomers. Based on the PCM model a value of 3.9 kJ mol^{-1} was obtained in solution corresponding well with the experimental result. The semiempirical AM1 calculations, although in rather good correspondence with the ab initio results for the tautomeric equilibria, give an incorrect description of the E/Z relation with the Z isomer as the most stable form.

Replacing the second oxygen atom by a nitrogen causes significant changes of the tautomeric equilibria. The results for the molecules maleic imidine **3** and phthalic imidine **6** (Fig. 3) given in Table 4 demonstrate that the energy differences between the amino–imino forms **3e** and **6e** and the various diimino forms are considerably lower than those for the corresponding compounds of maleimide and phthalimide, respectively. The 6-31G* results indicate the diimino forms still as most stable, but the amino–imino tautomers are comparable in energy now. The effects of electron correlation calculated at MP2 are again negligible. According to the AM1 calculations, the most stable

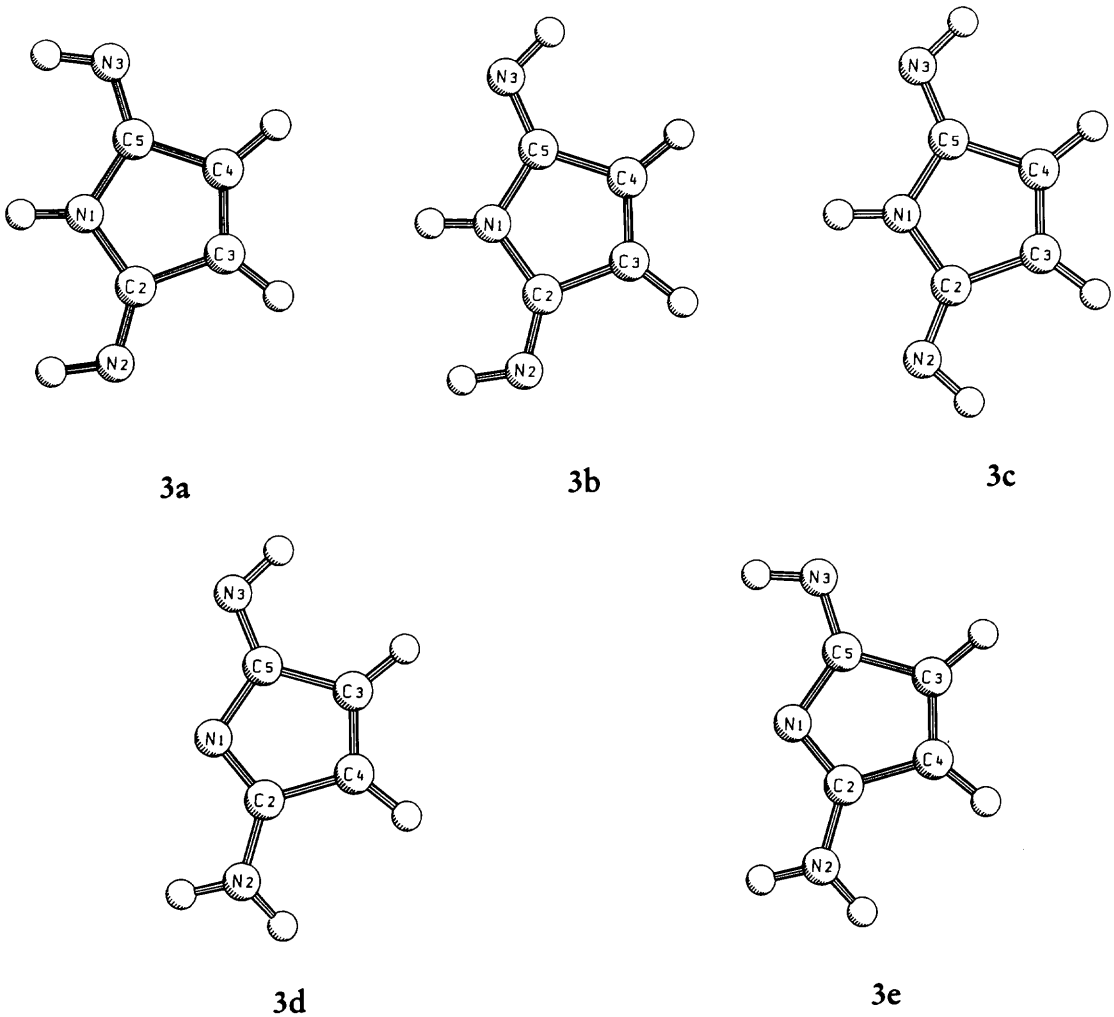

Fig. 3. The various tautomers of maleic imidine **3** (the corresponding tautomers of phthalic imidine **6** have an additional benzene ring annelated at the C_3-C_4 bond).

Table 4
Energy differences between the tautomers of 1*H*-pyrrol-2,5-diimine and phthalic imidine in the gas phase and in solution in kJ mol^{-1}

Tautomer	6-31G*			AM1	
	ΔE_g	ΔE_g (MP2)	ΔG_s^a	$\Delta\Delta H_f^\circ$	$\Delta\Delta H_{f,s}^{\circ\,b}$
Maleic imidine					
3a	4.5	6.1	8.1	0.0	0.0
3b	0.1	1.1	3.3	10.0	10.1
3c	0.0[c]	0.0[d]	0.0	22.5	23.3
3d	26.9	22.7	9.3	41.0	27.7
3e	4.9	4.3	7.0	17.7	5.2
Phthalic imidine					
6a	2.9		9.6	0.0	0.7
6b	0.0[e]		4.0	9.2	11.9
6c	1.9		0.0	20.6	23.0
6d	27.9		8.4	39.4	21.2
6e	5.2		6.8	17.3	0.0

[a] PCM formalism.
[b] CT model.
[c] E_g (6-31G*//6-31G*) = −317.70322 a.u.
[d] E_g (MP2/6-31G*//6-31G*) = −318.67490 a.u.
[e] E_g (6-31G*//6-31G*) = −470.37304 a.u.

diimino tautomers are still more preferred over the most stable amino–imino tautomer than given by ab initio MO theory, although the general tendency of additional stabilization of the amino–imino forms is correctly reflected. However, the stability order of the various diimino tautomers is reversed in comparison to the ab initio results.

According to the PCM and the CT model, the various tautomers are differently concerned by solvent influence. Based on the PCM formalism the amino–imino tautomers **3d** and **6d** gain the most stabilization. They are comparable with the alternative amino–imino tautomers **3e** and **6e** now. Thus, the importance of the amino–imino forms is documented in solution, although a slight preference of some diimino tautomers is still maintained. This tendency of the solvation influence is also reflected by the CT formalism. In the case of the amino–imino tautomer **6e** the calculated influence of the solvent is even so strong, that it becomes the most stable form of all. Although both solvation models agree in essential points of tautomerism in these series of compounds, there are sometimes considerable discrepancies in the description of the solvation of selected tautomers as illustrated by the data in Table 4. It is not easy to find the actual reasons for the differences in those particular cases.

The experimental results are somewhat contradictory. Whereas earlier UV data suggest phthalic imidine existing in the diimino form [10], recent NMR investigations find a predominance of the 3-amino-1*H*-isoindol-1-imine in DMSO and several other solvents [11]. In any case, experimental and theoretical results support the importance of the amino–imino forms in the tautomerism of maleic and phthalic imidines. In comparison to the lactam–lactim tautomerism, the possibility of amino–imino tautomerism has to be considered for this type of molecules.

4. Conclusions

The systematic analysis of tautomerism of maleimide and phthalimide derivatives based on ab initio and semiempirical MO theory indicates significant changes when replacing the oxygen atoms of maleimide and phthalimide by nitrogens. Whereas lactam–lactim tautomerism can be neglected in these systems, amino–imino tautomerism plays an important role in maleic and

phthalic imidines. The shift of the tautomeric equilibria in favour of the amino–imino tautomers is additionally supported by polar solvents. The influence of correlation effects on the tautomer stability is negligible for these systems. There are some discrepancies in the stability order of tautomers of the same type between ab initio and AM1 results. The AM1 results are inferior in comparison to the ab initio data, although essential points of tautomerism are correctly reproduced. Similar conclusions can be drawn when comparing the description of the solvent influence given by the PCM and the CT method. However, the PCM formalism seems to reflect the peculiarities of the electronic distribution in the molecules somewhat better than the CT model.

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References

[1] L. Le Gall, J. Lauransan and P. Saumagne, Can. J. Spectr., 20 (1975) 136.
[2] T. Woldbaek, P. Klaboe and C.J. Nielsen, J. Mol. Struct., 27 (1975) 283.
[3] A.J. Barnes, L. Le Gall, C. Madec and J. Lauransan, J. Mol. Struct., 38 (1977) 109.
[4] L. Le Gall and A.J. Barnes, Ber. Bunsenges, Phys. Chem., 82 (1978) 52.
[5] L. Le Gall, P. Caillet and M.T. Forel, J. Chim. Phys., 75 (1978) 444.
[6] L. Harsányi, E. Vajda and I. Hargittai, J. Mol. Struct., 129 (1985) 315.
[7] L. Harsányi, P. Császár, G.H. Fogarasi and I. Szilágyi, J. Mol. Struct., 104 (1983) 79.
[8] P. Császár, A. Császár, L. Harsányi and J.E. Boggs, J. Mol. Struct. (Theochem), 136 (1986) 323.
[9] M. Yu. Kornilov and V.P. Makovestskii, Ukr. Khim. Zh., 41 (1975) 933.
[10] P.F. Clark, J.A. Elvidge and J.H. Golden, J. Chem. Soc., (1956) 4135.
[11] L.I. Spiessens and M.J.O. Anteunis, Bull. Soc. Chim. Belg., 93 (1984) 459.
[12] R. Czerminski, B. Lesyng and A. Pohorille, Int. J. Quantum Chem., 16 (1979) 605.
[13] C. Krebs, H.-J. Hofmann, H.-J. Köhler and C. Weiss, Chem. Phys. Lett., 69 (1980) 537.
[14] J.S. Kwiatkowski, B. Lesyng, M.H. Palmer and W. Saenger, Z. Naturforsch, 37C (1982) 937.
[15] A. Les and I. Ortega-Blake, Int. J. Quantum Chem., 27 (1983) 567.
[16] A. Buda and A. Syguła, J. Mol. Struct. (Theochem), 121 (1985) 133.
[17] J.S. Kwiatkowski, T.J. Zielinski and R. Rein, Adv. Quantum Chem., 18 (1986) 85.
[18] P. Cieplak, P. Bash, U.C. Singh and P.A. Kollman, J. Am. Chem. Soc., 109 (1987) 6283.
[19] J.S. Kwiatkowski, R.J. Bartlett and W.B. Person, J. Am. Chem. Soc., 110 (1988) 2353.
[20] W.M.F. Fabian, Z. Naturforsch., 45A (1990) 1328.
[21] A. Syguła, J. Chem. Res. (S), (1989) 56.
[22] A.R. Katritzky, M.M. Karelson and P.A. Harris, Heterocycles, 32 (1991) 329.
[23] A.R. Katritzky and M.M. Karelson, J. Am. Chem. Soc., 113 (1991) 1561.
[24] M.M. Karelson, A.R. Katritzky, M. Szafran and M.C. Zerner, J. Org. Chem., 54 (1989) 6030.
[25] H.B. Schlegel, P. Gund and E.M. Fluder, J. Am. Chem. Soc., 104 (1982) 5347.
[26] H.B. Schlegel, Int. J. Quantum Chem., 22 (1982) 1041.
[27] M.J. Scanlan, I.H. Hillier and A.A. MacDowell, J. Am. Chem. Soc., 105 (1983) 3568.
[28] M.J. Scanlan and I.H. Hillier, Chem. Phys. Lett., 98 (1983) 545.
[29] W.J. Hehre, L. Radom, P.v.R. Schleyer and J.A. Pople, Ab initio Molecular Orbital Theory, Wiley, New York, 1986.
[30] S. Miertuš, E. Scrocco and J. Tomasi, Chem. Phys., 55 (1981) 117.
[31] M. Persico and J. Tomasi, Croat. Chim. Acta, 57 (1984) 1395.
[32] R. Bonaccorsi, R. Cimiraglia and J. Tomasi, J. Comput. Chem., 4 (1983) 567.
[33] J.L. Pascual-Ahuir, E. Silla, J. Tomasi and R. Bonaccorsi, J. Comput. Chem., 8 (1987) 778.
[34] M.A. Aguilar and F.J. Olivares del Valle, Chem. Phys., 129 (1989) 439.
[35] C.J. Cramer and D.G. Truhlar, J. Am. Chem. Soc., 113 (1991) 8305.
[36] C.J. Cramer and D.G. Truhlar, Science, 256 (1992) 213.
[37] C.J. Cramer and D.G. Truhlar, J. Comp. Aid. Mol. Des., 6 (1992) 69.
[38] M.J. Frisch, M. Head-Gordon, G.W. Trucks, J.B. Foresman, H.B. Schlegel, K. Raghavachari, M.A. Robb, J.S. Binkley, C. Gonzalez, D.J. DeFrees, D.J. Fox, R.A. Whiteside, R. Seeger, C.F. Melius, J. Baker, R.L. Martin, L.R. Kahn, J.J.P. Stewart, S. Topiol and J.A. Pople, GAUSSIAN 90, Gaussian Inc., Pittsburgh, PA, 1990.
[39] M. Dupuis, J.D. Watts, H.O. Villar and G.J.B. Hurst, HONDO, version 7.0, QCPE Program No. 544, University of Indiana, Bloomington IN, 1988.
[40] SPARTAN, version 3.0, Wavefunction Inc., Irvine CA, USA, 1993.

[41] K. Bösl, Thesis, University of Karlsruhe, Germany, 1968.
[42] J. Armand, S. Deswarte, J. Pinson and H. Zamarlik, Bull. Soc. Chim. France, (1971) 671.
[43] J. Elguero, C. Marzin, A.R. Katritzky and P. Linda, Adv. Heterocycl. Chem., Suppl. 1 (1976) 263.
[44] L.I. Spiessens and M.J.O Anteunis, Bull. Soc. Chim. Belg., 92 (1983) 965.