JOURNAL OF PHYSICAL ORGANIC CHEMISTRY
J. Phys. Org. Chem. 2001; **14:** 566–576
DOI:10.1002/poc.412

Tautomerism in 4-substituted 1-phenyl-3-methyl-pyrazolin-5-ones—a theoretical *ab initio* and ^{13}C NMR study

E. Kleinpeter* and A. Koch

Institut für Organische Chemie und Strukturanalytik, Universität Potsdam, P.O. Box 60 15 53, D-14415 Potsdam, Germany

Received 27 February 2001; revised 23 April 2001; accepted 8 May 2001

epoc ABSTRACT: The tautomeric equilibria between the CH, OH and NH forms in a series of 4-substituted 1-phenyl-3-methyl-pyrazolin-5-ones have been studied using *ab initio* calculations at various levels of theory and comparison made with the experimental results obtained from NMR measurements. Quantitative comparison of both the relative energies and the ^{13}C chemical shifts of the tautomers constituting the tautomeric equilibria were made by calculation of both sets of parameters. The influence of the solvent was included by employing various models of the self-consistent reaction field theory. Initially, the solvent was included in the calculations by applying a continuum of differing polarity over the surface of isolated tautomers (self-consistent isodensity polarized continuum model method), then later by assuming formation of an adduct between the solute and the solvent (thereby simulating effectively the hydrogen bonding in the OH and NH tautomers) and finally by calculating dimer or trimer complexes of the various tautomers. In this manner, the agreement between the theoretically calculated and the experimentally determined tautomeric equilibria was improved significantly. The theoretically calculated ^{13}C chemical shifts of the tautomers were found to be viable for the assignment of the tautomers, particularly the preferred tautomer in the OH/NH equilibrium, which remains fast on the NMR time scale even at low temperatures. Copyright © 2001 John Wiley & Sons, Ltd.

Additional material for this paper is available from the epoc website at http://www.wiley.com/epoc

KEYWORDS: substituted 1-phenyl-3-methyl-pyrazolin-5-ones; *ab initio* calculations; NMR spectroscopy; ^{13}C chemical shifts; tautomeric equilibria; solvent influence; intermolecular interactions

INTRODUCTION

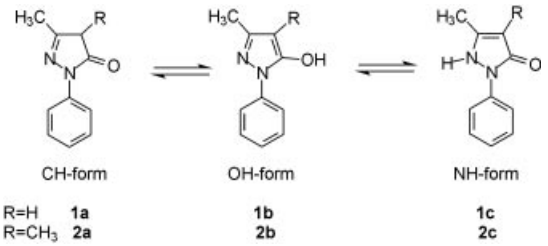
The study and quantitative evaluation of prototropic tautomerism in heterocyclic compounds, which continues to be of primary interest for both the reactivity and the reaction pathway taken by these compounds, can only be properly understood if the contributions of all possible tautomers to the equilibrium are effectively quantified as opposed to simply assessing the likely, preferred tautomeric structure. The implications of this type of work can have immense value, for example, for biological systems where the tautomeric form of the nucleic acid bases is determinate for base pairing, which then consequently determines the frequency of mutations.

The prototropic tautomerism in 4-alkyloxy- and 4-alkylthio-1-phenyl-3-methyl-pyrazolin-5-ones,[1] 4-benzoyl- and 4-cinnamoyl-1,3-dimethyl-pyrazolin-5-ones,[2] various rubazoic acid derivatives[3] and 1-phenyl-3-methyl-4-(1-phenyl-3-methyl-pyrazolin-5-yl)-3-pyrazolin-5-one[4] were all studied in various solvents. In the case of fast equilibria, estimations of the equilibrium position were based on reference compounds[4] or on solid-state cross-polarization and magic angle spinning (CP-MAS) NMR measurements[1–3] supported initially by force field[1] or semi-empirical quantum-chemical calculations.[3,5,6] These have been reviewed by Katritzky *et al.*[7] Subsequently, the more sophisticated methods of *ab initio* molecular orbital (MO) theory were employed. For example, the tautomerism of 3-hydroxy-pyrazole has been studied by high-level *ab initio* quantum mechanical methods in both the gas phase and in aqueous solution, where the NH tautomer was indicated to be more stable than the OH tautomer.[8] The result compared favourably with experiment in the gas phase,[9] but not so in aqueous solution.[10] Importantly, *N*-substituted pyrazoles,[11] 3-nitropyrazole[12] and 5-ethoxycarbonyl-3-hydroxy-pyrazole[13] were also calculated using *ab initio* methods in the gas phase and included electron correlation. The preferred tautomer implicated in each case was that which was also found experimentally both in the solid state by CP-MAS NMR and also in solution.

The prototropic tautomerism of both 1-phenyl-3-methyl-pyrazolin-5-one (**1**) and its 4-methyl derivative (**2**) has been extensively studied in the gas phase, in solution and in the solid state.[14–16] Depending on the

**Correspondence to:* E. Kleinpeter, Institut für Organische Chemie und Strukturanalytik, Universität Potsdam, P.O. Box 60 15 53, D-14415, Potsdam, Germany.

Copyright © 2001 John Wiley & Sons, Ltd.



Scheme 1. The three tautomeric forms of **1** and **2**

Scheme 2. The structures of the seven compounds comprising this tautomeric study

solution, the three possible tautomers, the CH form **1,2a**, the OH form **1,2b** and the NH form **1,2c** (see Scheme 1), can all be found. The rate of interconversion between the CH tautomer **1,2a** and the other two tautomers, **1,2b** and **1,2c**, is sufficiently slow on the NMR time scale for separate sets of signals to be observable whereas the rate of interconversion between the NH and the OH forms, **1,2b** and **1,2c**, was found to be too fast on the NMR time scale and only averaged signals are observed, even at low temperatures.[17–22] In $CDCl_3$ solution, it is the tautomer **2a** that dominates,[14–19] but in d_6-DMSO the preference shifts towards the equilibrium **2b** $\rightleftharpoons$ **2c**. The position of the equilibrium **2b** $\rightleftharpoons$ **2c**, though, could only be estimated by the use of reference compounds.[14–19]

Since it is not possible currently to freeze out the NH/OH tautomeric equilibrium in **1,2b** and **1,2c**, a high-level *ab initio* MO study on the tautomerism in **1** and **2** and a number of other 4-substituted 1-phenyl-3-methyl-pyrazolin-4-ones (**3–7**, see Scheme 2) was thus warranted to validate the previous estimations. Moreover, the tautomeric equilibrium was modelled in solution to enable direct comparison with the results from NMR measurements; to this effect, it was required to include the influence of the solvent in the calculations, and efforts were also made to model intermolecular interactions between the tautomers and the solvent molecules. Herein, the results of this *ab initio* study, together with the ^{13}C NMR results, are reported.

RESULTS AND DISCUSSION

Ab initio calculation of the tautomeric equilibria in 1–7 at various levels of theory

Since the tautomeric equilibria of both **1** and **2** have been extensively studied experimentally in various solvents, the energies of the tautomers for these two compounds were calculated using *ab initio* methods at different levels of theory—HF/6-31G*, HF/6-31G**, HF/6-311G**, HF/6-311 + G**,[23] MP2/6-31G**[24]—including the density functional theory (DFT) approach at level B3LYP/6-311G**[25] (these latter two included the effect of electron correlation), in order to evaluate the most appropriate methodology for the additional compounds (**3–7**). Thermodynamic corrections were also incorporated in these computations. The results of these calculations are presented in Table 1, including both the relative total energies of the tautomers and the torsion angles between the planes of the pyrazolin-5-one ring and the *N*-phenyl ring. The torsion angle was calculated to provide an indication of the level of conjugation in the compounds and the influence of the substituent at position 4 on one characteristic structural property. Based on these calculations, the following points for further calculations on the other 4-substituted 1-phenyl-3-methyl-pyrazolidin-5-ones **3–7** are noted.

(i) Both zero-point vibration and thermodynamic corrections have only a negligible effect on determining the relative stability of the various tautomers, and they are essentially independent of the level of computation:

comp. **1**	**a**	**b**	**c**
(HF/6-31G*/kcal mol^{-1})	(100.06)	(100.82)	(101.28)
comp. **1**	**a**	**b**	**c**
(B3LYP/6-311G**/kcal mol^{-1})	(90.98)	(91.28)	(91.48)

(ii) The application of polarization functions for the hydrogen atoms (particularly with regard to hydrogen bonding) stabilizes the OH tautomers by *ca* 3 kcal mol^{-1} and the NH tautomers by *ca* 1.5 kcal mol^{-1} in comparison with the CH tautomer.

(iii) The largest variation in the relative total energies of the tautomers was obtained after inclusion of electron correlation; the OH tautomer was stabilized by 4.7–7.3 kcal mol^{-1} and the CH tautomer by 0–2.2 kcal mol^{-1} in comparison with the NH tautomer. Both the π-electron excess character of the five-membered heterocyclic ring and the extended conjugation along the entire mesomeric system of the 3,4-disubstituted 1-phenyl-pyrazolin-5-one were responsible for this result.

(iv) For the various calculations, different starting structures for the tautomers were utilized and, independent of the applied level of theory, the same global energy minimum structure was arrived at in each case. Thus, for finding the global minima of the tautomers, even the lowest level of computation was sufficiently adequate.

Thus, computations at levels of HF/6-31G*, MP2/6-31G** and DFT at level B3LYP/6-311G** were employed to study the tautomerism of **3–7**; the relative energies and the corresponding torsion angles are also presented in Table 1. (The positions of the tautomeric

Copyright © 2001 John Wiley & Sons, Ltd.

Table 1. Relative energies and torsion angles between the planes of the pyrazolinone ring and the *N*-phenyl ring for the tautomeric forms of the 4-substituted 1-phenyl-3-methyl-pyrazolin-5-ones **1–7**

	CH form		OH form		NH form	
Molecule/method	Rel. energy (kcal mol^{-1})	Torsion angle (deg)	Rel. energy (kcal mol^{-1})	Torsion angle (deg)	Rel. energy (kcal mol^{-1})	Torsion angle (deg)
1[a] **4-H**						
HF/6-31G*	0.0	–	12.0	–	8.6	–
HF/6-31G*[G#]	0.0	–	12.7	–	9.8	–
HF/6-31G**	0.0	–	8.6	–	7.2	–
HF/6-311G**	0.0	–	8.2	–	6.4	–
HF6-311 + G**	0.0	–	8.1	–	6.1	–
B3LYP/6-311 + G**	0.0	–	6.9	–	5.4	–
B3LYP/6-311 + G**[G#]	0.0	0.0	7.2	22.4	5.9	8.3
MP2/6-31G**	0.0	7.1	4.1	32.9	8.5	9.5
2[b] **4-CH$_3$**						
HF/6-31G*	0.0	–	11.6	–	6.5	–
HF/6-31G*[G#]	0.0	–	11.5	–	6.9	–
HF/6-31G**	0.0	–	8.5	–	5.1	–
HF/6-311G**	0.0	–	8.6	–	4.6	–
HF/6-311 + G**	0.0	–	8.6	–	4.6	–
B3LYP/6-311 + G**	0.0	0.7	5.9	31.1	3.0	8.0
MP2/6-31G**	0.0	5.4	3.1	34.0	6.3	8.5
3[b] **4-Br**						
HF/6-31G*	0.0	–	7.6	–	7.4	–
B3LYP/6-311 + G**	0.0	7.1	2.5	25.1	3.5	12.6
MP2/6-31G**	0.0	17.0	0.3	32.3	7.1	11.4
4[c] **4-NO$_2$**						
HF/6-31G*	7.3	–	0.0	–	11.3	–
B3LYP/6-311 + G**	11.5	8.4	0.0	23.4	12.0	17.0
MP2/6-31G**	10.2	19.6	0.0	32.1	16.5	14.4
5[c] **4-SCN**						
HF/6-31G*	0.0	–	1.1	–	2.4	–
B3LYP/6-311 + G**	1.7	5.1	0.0	28.8	2.0	14.0
MP26-31G**	3.3	19.8	0.0	34.1	7.5	13.2
6[d] **4-CO—CH$_3$**						
HF/6-31G*	7.3	–	0.0	–	6.8	–
B3LYP/6-311 + G**	10.3	1.8	0.0	16.5	7.7	14.4
MP2/6-31G**	10.3	15.4	0.0	29.2	12.7	12.6
7[c] **4-NH—CO—CH$_3$**						
HF/6-31G*	0.0	–	4.5	–	4.6	–
B3LYP/6-311 + G**	3.9	0.4	0.0	22.5	3.1	10.6
MP2/6-31G**	5.9	8.5	0.0	31.6	3.3	10.0

[a] In d_6-DMSO: OH form (major); CH form (minor); in $CDCl_3$: CH form (major), NH form (minor).[19]
[b] In d_6-DMSO: OH form (preferred); in $CDCl_3$: CH form (major), NH form (minor).[19]
[c] In d_6-DMSO: OH form preferred.[19]
[d] In both d_6-DMSO and $CDCl_3$ the OH form is preferred.[26,27]

equilibria in **1–7** are also provided, as determined experimentally by NMR in various solvents.[19,26,27])

The calculated relative stability of the tautomers proved to be dependent on the substituent located in position 4. Only in the case of **4** and **6** was the OH form, **4,6b**, found to be the most stable tautomer, in agreement with experiment; the presence of intramolecular hydrogen bonding between the 4-substituent and the OH stabilizes **4,6b** sufficiently that even rudimentary calculation at the HF/6-31G* level indicated this correctly. Upon including electron correlation (MP2/6-31G** or B3LYP/6-311G** level), the OH tautomer was also calculated to be the most stable tautomer for both **5** and **7** (as is found experimentally in solution); calculation at the HF/6-31G* level provided the corresponding CH analogue as the most stable tautomer for **5** and **7**. Finally, in **1–3** the CH tautomer was calculated to be the preferred tautomer in the tautomeric equilibria; this is in line for **1** in $CDCl_3$ solution, but is in contrast to what is found for both **2** and **3** in solution. In **2** and **3**, when including electron correlation, the OH form was also indicated to be more stable than the NH form. This, too, is in disagreement with NMR measurements, although the NMR results are equivocal[19,26,27] because they are estimations based on

Copyright © 2001 John Wiley & Sons, Ltd.

reference compounds. This equilibrium between the OH and NH forms is fast on the NMR timescale, even at low temperatures, and, therefore, it was decided to study in more detail theoretically both the influence of the solvent on the tautomeric equilibria and the influence of intermolecular hydrogen bonding between the tautomer and the solvent or between various OH/NH tautomers. Previously, Dardonville *et al.*[21] had found the CH form of 1-(2′,4′-dinitrophenyl)-3-methyl-2-pyrazolin-5-one to be the most stable tautomer at all levels of theory, although all three tautomers could be detected in solution and the proportion of the CH form varied according to the solvent.

The geometry of the pyrazolinone ring was indicated to be planar in both the CH and the OH tautomers; in the NH tautomer N-2 was determined to be slightly pyramidal. The highest torsion angle between the two ring moieties was calculated for the OH tautomer in every case (17–34°), with the torsion angles in the NH and CH tautomers always much smaller and generally comparable to one another. It can be inferred, though, that with only slight angles present in all cases, a considerable degree of conjugation between the two ring systems is always in existence.

As an experimental probe for assessing the degree of interannular conjugation for pyrazolinones in solution, Begtrup[28] utilized the chemical shift of the phenyl *ortho* carbon and its difference to the chemical shift of the *meta* carbon. When full conjugation is in effect, the chemical shift of the *ortho* carbon lies in the restricted range of 118.5–118.8 ppm and the chemical shift difference from the *meta* carbon ($\Delta\delta_{m-o}$) is equal to 10.5 ppm. Deshielding of the *ortho* carbon and consequent reduction in $\Delta\delta_{m-o}$ results from increasing degrees of twist between the ring planes. From literature values available for the carbon chemical shifts, the degrees of twist as indicated by the *ab initio* calculations here are substantiated. In fact, for **3** the ^{13}C NMR spectra of all three tautomers are known and the results (for the CH form, $\delta_o = 118.9$ ppm, $\Delta\delta_{m-o} = 9.3$ ppm; NH form, $\delta_o = 120.6$ ppm, $\Delta\delta_{m-o} = 8.4$ ppm; OH form, $\delta_o = 121.2$ ppm, $\Delta\delta_{m-o} = 7.7$ ppm) are in complete agreement with the theoretically calculated twist angles. In other cases also where more than one tautomer is present in the tautomeric equilibrium, the calculated results are corroborated by the ^{13}C chemical shift parameters.[19]

Ab initio calculation of the tautomeric equilibria of 1–7 including solvent effects

Since the tautomeric equilibrium of the 1-phenyl-pyrazolin-5-ones is dependent on the solvent, the temperature and the concentration, it is quite evident that intermolecular interactions between the tautomers themselves and/or with the solvent are in effect, and most probably these interactions are of a hydrogen bonding nature.[19,22] The interactions with the solvent can readily be taken into consideration in these computations by including the self-consistent reaction field (SCRF) technique into the *ab initio* calculations.[29,30] In this technique the solvent is considered as a polar continuum on the surfaces of the tautomers and specific interactions between the solute tautomers and the solvent molecules are not calculated, *i.e.* for hydrogen bonding only the electrostatic portion is evaluated whilst charge transfer is neglected. A number of test calculations were performed on compound **1** to assess an appropriate methodology to use, and because similar volumes for the tautomers were obtained from isoelectron densities at the HF/6-31G* level and only minor changes in bond lengths (<0.2 Å) were found along the solution calculations, single-point HF/6-31G* calculations employing the self-consistent isodensity polarized continuum model (SCIPCM)† were conducted on **1**–**7** for each of the three tautomeric forms. The relative energies of the tautomers and the solvation energies are presented in Table 2.

The NH tautomers were indicated to have the largest solvation energies, whereas those of CH and OH forms were generally quite comparable. The solvation energies in DMSO, as expected, are larger in comparison with chloroform, although the general sequence of stabilization was not altered. Owing to the stronger solvation of the NH form with respect to CH and OH forms, the experimentally observed sequence of the tautomers in **1**–**3** in chloroform (see Table 1) is now correctly predicted by these calculations. However, in DMSO the same sequence was again predicted, which is in disagreement with experiment. The tautomeric preference for compounds **4** and **6**, the OH tautomer, is again correctly indicated. However, the correct order of the tautomeric preference for **5** and **7**—as obtained when including electron correlation but not solvent interactions—cannot be reproduced with these SCIPCM-HF/6-31G* calculations. For **5** and **7** the NH and CH tautomers respectively are indicated as the preferred tautomers, both of which are in disagreement with the NMR results.

This inconsistency, especially the stabilization of the OH tautomer (by experiment) with respect to the NH tautomer in **5**, induced us to consider further influences that must be stabilizing the OH tautomer and which have not been sufficiently incorporated into the SCIPCM-HF/6-31G* calculations. Thus, 1:1 adducts comprised of tautomer and solvent were calculated in order to simulate the influence of potential intermolecular hydrogen bonds between the NH or OH groups and the DMSO molecules, in the respective tautomers. Of course, similar hydrogen bonds cannot be present in the CH tautomers and significant changes to the resultant relative energies were anticipated. The results of various calculations performed on **1** are presented in Table 3. To properly assess the

†T. A. Keith, J. B. Foresman and M. J. Frisch SCIPCM algorithm by, part of the GAUSSIAN 94 package, see Ref. 31.

Copyright © 2001 John Wiley & Sons, Ltd.

Table 2. Relative energies of the tautomers of **1–7** and the corresponding solvation energies of $CHCl_3$ ($\varepsilon = 4.81$) and DMSO ($\varepsilon = 46.7$) calculated using the SCIPCM-HF/6-31G* method

	CH form		OH form		NH form	
Molecule	Rel. energy (kcal mol^{-1})	Solv. energy (kcal mol^{-1})	Rel. energy (kcal mol^{-1})	Solv. energy (kcal mol^{-1})	Rel. energy (kcal mol^{-1})	Solv. energy (kcal mol^{-1})
1 4-H						
$CHCl_3$	0.0	−4.9	11.5	−5.4	7.0	−6.6
DMSO	0.0	−6.9	10.9	−7.9	6.2	−9.3
2 4-CH_3						
$CHCl_3$	0.0	−4.5	11.5	−4.6	5.3	−5.7
DMSO	0.0	−6.4	11.1	−7.0	4.7	−8.2
3 4-Br						
$CHCl_3$	0.0	−4.6	8.2	−4.1	5.2	−6.8
DMSO	0.0	−6.7	8.6	−5.7	4.7	−9.8
4 4-NO_2						
$CHCl_3$	6.2	−6.2	0.0	−5.1	5.4	−11.1
DMSO	5.7	−8.8	0.0	−7.3	2.7	−15.9
5 4-SCN						
$CHCl_3$	0.4	−6.7	1.8	−6.3	0.0	−9.5
DMSO	1.5	−9.6	3.1	−9.0	0.0	−13.5
6 4-$COCH_3$						
$CHCl_3$	6.1	−5.4	0.0	−4.3	3.6	−7.4
DMSO	5.5	−7.8	0.0	−6.1	2.2	−10.7
7 4-$NHCOCH_3$						
$CHCl_3$	0.0	−6.7	4.7	−6.4	3.5	−7.8
DMSO	0.0	−9.6	4.7	−9.4	3.2	−11.0

adducts, different positions of DMSO with respect to **1a–c** were selected and subjected to computation. Several different local minima were found, and the most stable ones (obtained from MP2/6-31G** calculations) are depicted in Fig. 1. At this level (MP2/6-31G**, *i.e.* including electron correlation), the experimentally observed tautomeric equilibrium is correctly calculated.

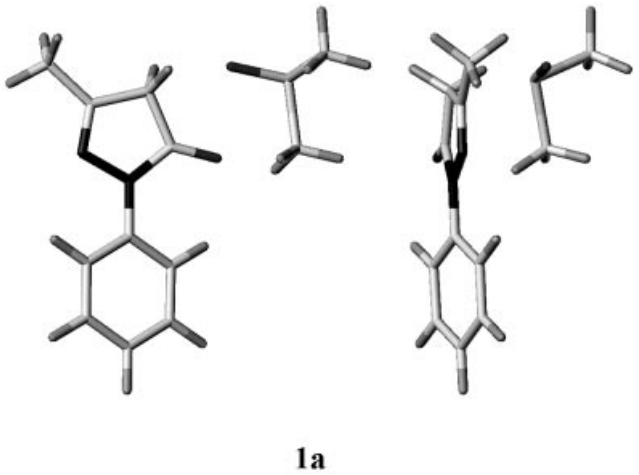
Quite obviously, hydrogen bonding is the preponderant intermolecular interaction in the tautomeric equilibria; however, intermolecular hydrogen bonds can also exist between OH tautomers or NH tautomers or a mix of the two, and this too can effect the position of the tautomeric equilibria. Adducts comprised solely of solute molecules based on hydrogen bonding are experimentally implied by the concentration and temperature dependence of the tautomeric equilibria being maintained even in chloroform solution. Indeed, intermolecular hydrogen bonding has been reported previously for the pyrazolinones in the solid state[12,20] and high-level *ab initio* calculations have been performed on the pyrazole cyclic dimer, trimer and tetramers in order to simulate intermolecular hydrogen bonding. The results were found to compare favourably[32] with experimental data from X-ray crystallography and solid-state NMR. Thus, in solution also, the pyrazolinones **1–7** should still be able to permeate intermolecular hydrogen bonds, resulting in significant stabilization of the corresponding tautomeric form(s).

Table 3. Relative energies of the tautomers of **1** (4-H) as a 1:1 adduct with DMSO at various levels of theory (HF/MP2) and the solvent regarded as an SCRF ($CDCl_3$, $\varepsilon = 4.81$; DMSO, $\varepsilon = 46.7$). All calculations were obtained by applying the 6-31G** basis set

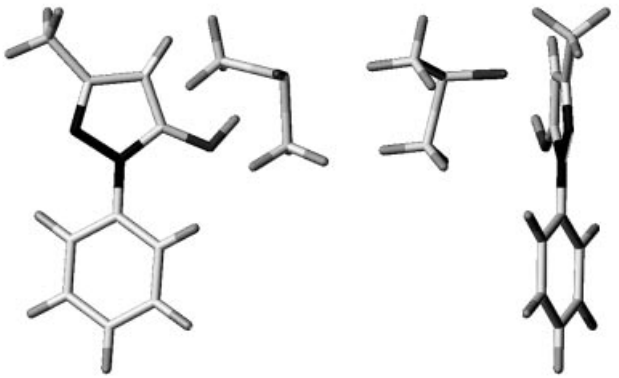
	Rel. energy (kcal mol^{-1})		
Method	CH form	OH form	NH form
HF/6-31G**	0.0	2.3	3.1
MP2/6-31G**	2.3	0.0	3.8
SCIPCM/4.81; HF6-31G**	0.0	5.0	3.1
SCIPCM/46.7; HF6-31G**	0.0	4.8	2.6

As previously, adducts of various starting geometries were selected for **1a–c** and calculations initially performed using the smaller basis set 3-21G, the structures thus obtained were then further optimized using the advanced basis set 6-31G**. Depicted in Figs 2 and 3 respectively are the most stable dimers and trimers of **1a–c**, and presented in Table 4 are the corresponding stabilization energies. The results obtained are in line with experiment, and although intermolecular hydrogen bonding is possible only between the OH and the NH tautomers, stabilization upon agglomeration also occurs to some degree, albeit far less in magnitude by comparison, for the CH tautomer. The OH tautomer is somewhat more effective than the NH form by comparable amounts for both the formation of dimers and of trimers, by

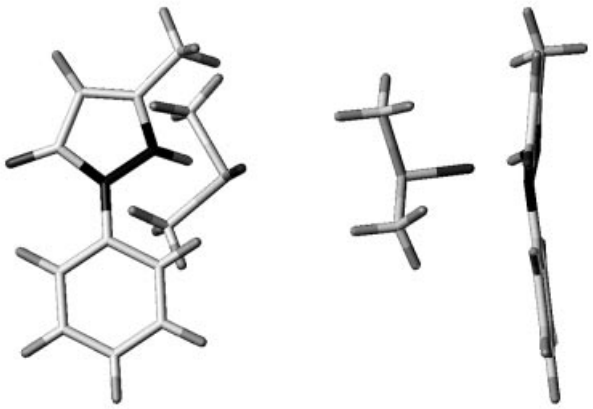
Copyright © 2001 John Wiley & Sons, Ltd.



1a



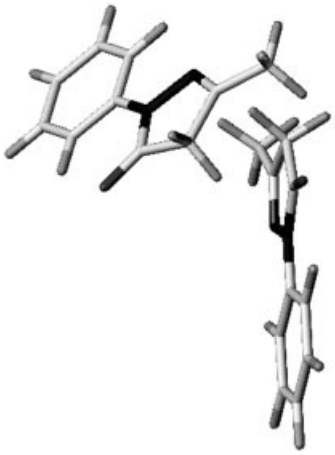
1b



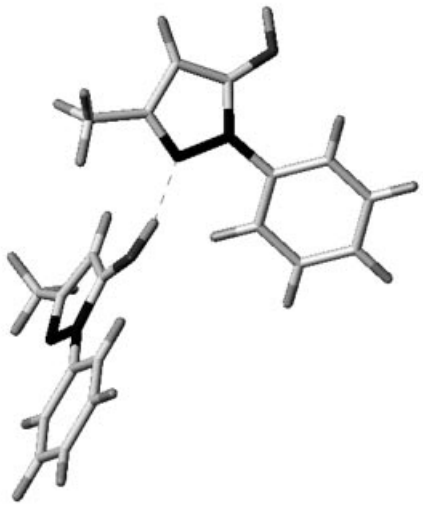
1c

Figure 1. Adducts of **1a–c** with one solvent molecule, DMSO, as obtained by *ab initio* calculations at the MP2/6-31G** level (orthographic view)

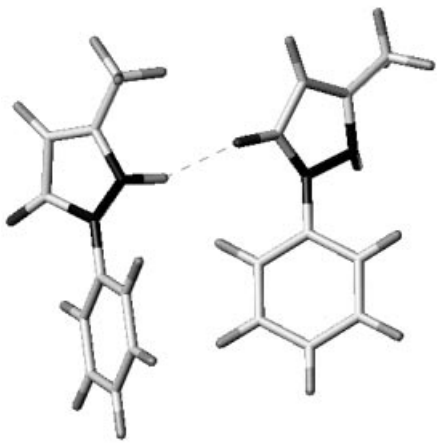
1.6 kcal mol^{-1} and 1.7 kcal mol^{-1} respectively. In addition, the basis set superposition error (BSSE) was calculated for correcting the intermolecular interaction energies (ΔE) between the dimers and trimers, and, as



1a



1b



1c

Figure 2. Dimeric structures of tautomers **1a–c**

Copyright © 2001 John Wiley & Sons, Ltd.

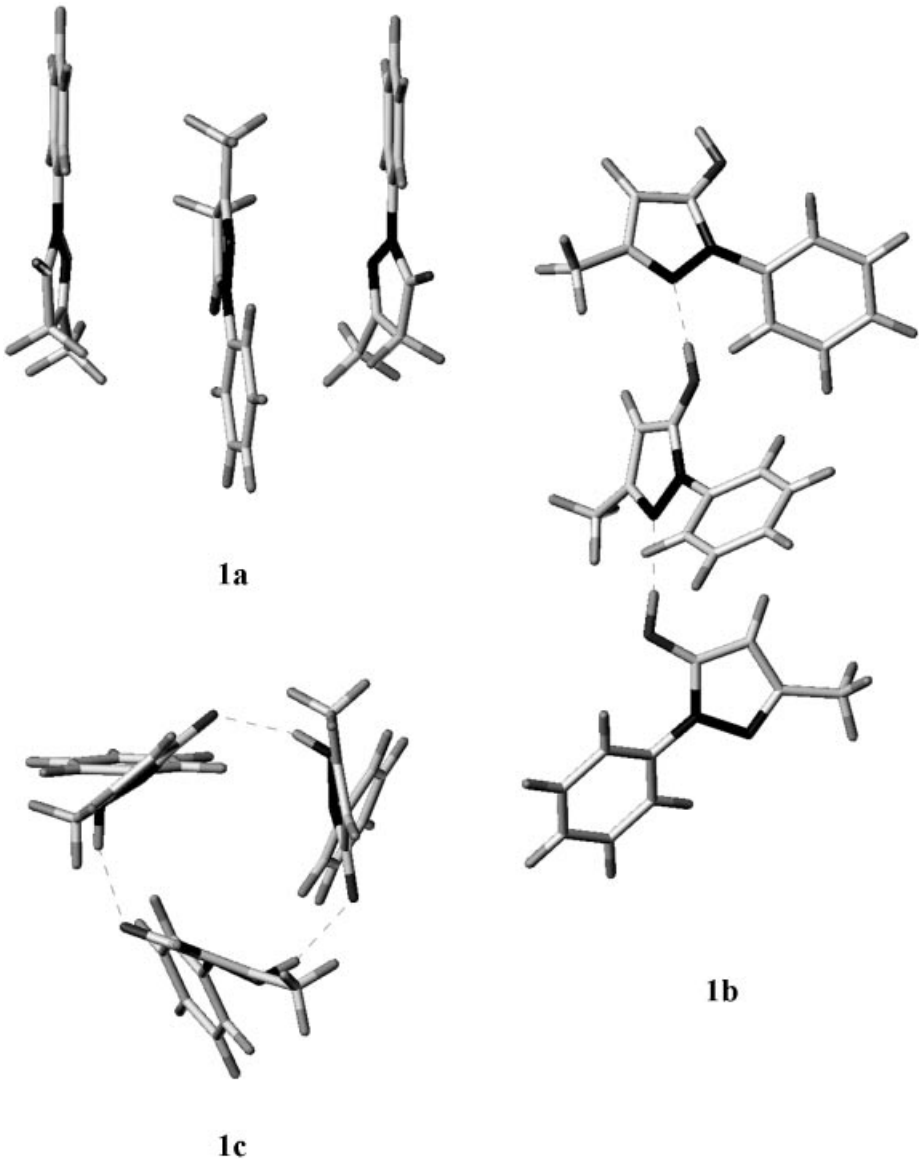


Figure 3. Trimeric structures of tautomers **1a–c**

expected, smaller BSSE values were obtained with the more sophisticated basis set 6-31G**.

The interaction energies calculated for the dimers and trimers describe much better the experimental tautomeric equilibria than all of the aforementioned high-level *ab initio* calculations at the same level of theory. However, significant improvements were also made by high-level *ab initio* calculations including electron correlation and by considering interactions of the solute with the solvent; thus, only by incorporating all of these aspects together, *i.e*. adducts comprised of dimers or trimers together with interactions with solvent (*e.g*. DMSO) at a level including electron correlation, would it be possible to quantify the tautomeric equilibria of pyrazolinones in solution accurately. These calculations, unfortunately, cannot presently be realized with the available equipment.

Calculation of the ^{13}C chemical shifts of the carbon atoms of 1–7 using the GIAO method

Whilst evaluating the energetics of the tautomeric equilibria of **1–7**, the corresponding ^{13}C chemical shifts of all carbon nuclei were calculated using the gauge-including atomic orbital (GIAO) perturbation method, which is incorporated as part of the GAUSSIAN 98 program. The resultant ^{13}C NMR spectra of the different tautomers were compared with the experimental spectra and the positions of the tautomeric equilibria assessed accordingly. This is straightforward for the CH tautomer because C-4 is sp^3 hybridized and exchange with the NH and OH tautomer is slow on the NMR timescale. For the equilibrium between the NH and OH tautomers, the rate of exchange is fast on the NMR timescale even at low temperatures, and comparison of the weighted average of

Copyright © 2001 John Wiley & Sons, Ltd.

Table 4. Total energies (in a.u.) and stabilization energies of the tautomers ΔE/BSSE (in kcal mol^{-1}) of **1a–c** due to the formation of dimers or trimers

Tautomers/Method	Monomer	Dimer	Trimer	ΔE_{Dimer}	$BSSE_{Dimer}$	ΔE_{Trimer}	$BSSE_{Trimer}$
1a							
HF/3-21G	−565.0773	−1130.1683	−1695.2563	−3.1	6.3	−5.3	11.6
HF/6-31G**	−568.2729	−1136.5540	−1704.8337	−3.0	2.3	−5.8	4.1
1b							
HF/3-21G	−565.0638	−1130.1535	−1695.2467	−11.9	6.3	−25.7	13.2
HF/6-31G**	−568.2592	−1136.5338	−1704.8120	−9.3	2.0	−21.8	4.9
1c							
HF/3-21G	−565.0697	−1130.1613	−1695.2561	−8.8	6.4	−20.1	13.0
HF/6-31G**	−568.2614	−1136.5370	−1704.8220	−7.7	2.0	−20.1	5.9

the NH and OH chemical shifts with those of the single tautomers was required for an indication of the position of the NH/OH equilibrium. ^{15}N and ^{13}C chemical shifts of the tautomers of some six- and five-membered heterocyclic compounds have been calculated by the same method and used as additional proof for the predominant tautomers.[33,34] The ^{1}H chemical shifts were not included in the present estimations because the chemical shift range of ^{1}H is small in comparison with the ^{13}C nucleus, and the solvent often has a direct and dramatic influence on the ^{1}H chemical shifts.

Likewise, employing all of the methods evaluated for consideration of the influence of the solvent **1** was used as a test case and the ^{13}C chemical shifts of the pyrazolinone carbon atoms were calculated. Both the experimental and the calculated ^{13}C chemical shifts, together with the corresponding deviations (Δδ/% and the sum of the deviations for C-3−C-5 as $\Delta\delta^2$) are presented in Table 5. At the HF/6-31G** level of theory, the deviations of the theoretical chemical shift values from experimental are comparable in the three tautomers and could not be reduced sufficiently by the inclusion of electron correlation, solvent interactions or agglomeration. On this basis, calculation at the HF/6-31G** level was deemed appropriate and the ^{13}C NMR spectra of **2–7** were calculated. The experimental and theoretical ^{13}C chemical shifts of the OH/NH forms of the pyrazolin-5-ones **1–7** are compared graphically in Figs 4–6.

The CH tautomer is easily identifiable by the high-field position of C-4, and this is in contrast to the corresponding carbon in the NH/OH tautomers, which appears at much lower field. C-5 and C-3 in the CH tautomer are

Table 5. Experimental and theoretical ^{13}C chemical shifts of the tautomers of **1** together with the deviation for each carbon atom (Δδ) and the sum of all three deviations ($\Delta\delta^2$)

	δ (ppm)			Δδ (%)			
Method	C3	C4	C5	C3	C4	C5	Sum ($\Delta\delta^2$)
1a, experimental	**156.4**	**43.0**	**170.5**				
Monomer **1a** HF	150.7	38.9	166.2	−3.6	−9.5	−2.5	110.6
Monomer **1a** B3LYP	161.8	46.5	174.4	3.5	8.1	2.3	83.4
Monomer **1a** MP2	140.2	40.5	158.3	−10.4	−5.8	−7.2	192.3
Monomer/DMSO **1a**	154.6	39.3	170.3	−1.2	−8.6	−0.1	75.4
Dimer **1a**	154.2	37.6	166.9	−1.4	−12.6	−2.1	164.1
Trimer **1a**	157.1	39.7	170.6	0.4	−7.7	0.1	59.1
1b, experimental	**148.5**	**89.0**	**155.2**				
Monomer **1b** HF	149.0	78.5	148.4	0.3	−11.8	−4.4	158.5
Monomer **1b** B3LYP	155.4	91.1	158.9	4.6	2.4	2.4	32.8
Monomer **1b** MP2	132.0	83.8	139.2	−11.1	−5.8	−10.3	263.9
Monomer/DMSO **1b**	149.9	78.1	150.4	0.9	−12.2	−3.1	160.4
Dimer **1b**	157.1	78.8	153.7	5.8	−11.5	−1.0	165.8
Trimer **1b**	154.7	78.0	153.7	4.2	−12.4	−1.0	171.1
1c, experimental	**148.6**	**92.3**	**160.4**				
Monomer **1c** HF	156.8	100.8	162.5	5.5	9.2	1.3	117.0
Monomer **1c** B3LYP	159.8	110.4	168.4	7.5	19.6	5.0	466.2
Monomer **1c** MP2	140.1	99.7	153.3	−5.7	8.0	−4.4	116.6
Monomer/DMSO **1c**	160.8	96.4	164.0	8.2	4.4	2.2	92.2
Dimer **1c**	158.8	97.2	167.2	6.9	5.3	4.2	93.3
Trimer **1c**	163.9	95.1	166.9	10.3	3.0	4.1	131.6

Copyright © 2001 John Wiley & Sons, Ltd.

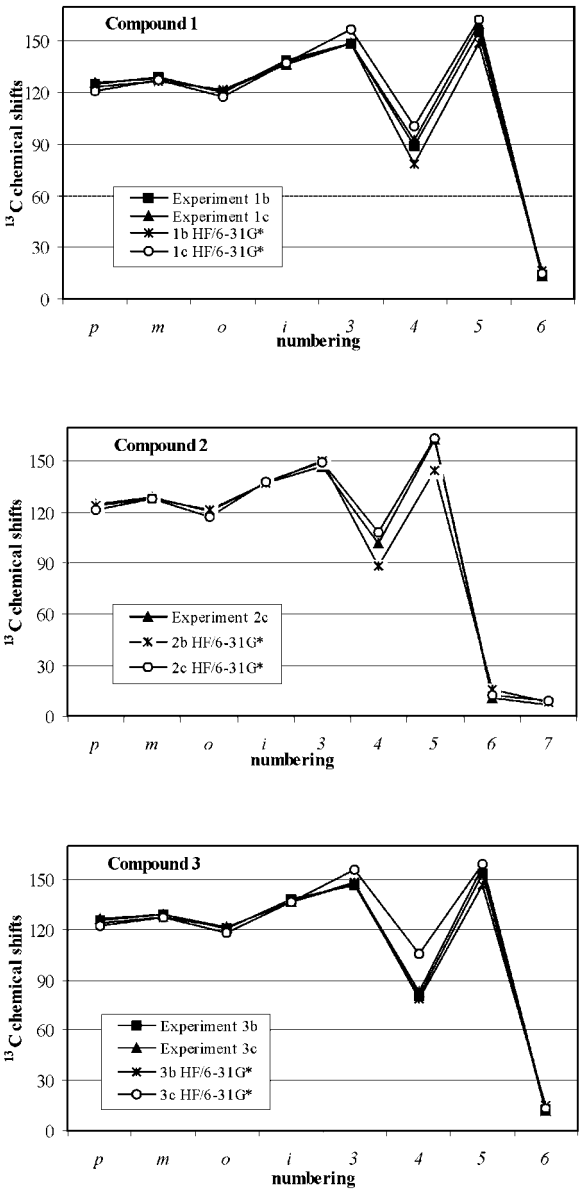


Figure 4. Experimental ^{13}C chemical shifts of the tautomers of **1**–**3** compared with the theoretically calculated shift values for fast NH/OH tautomeric interconversion

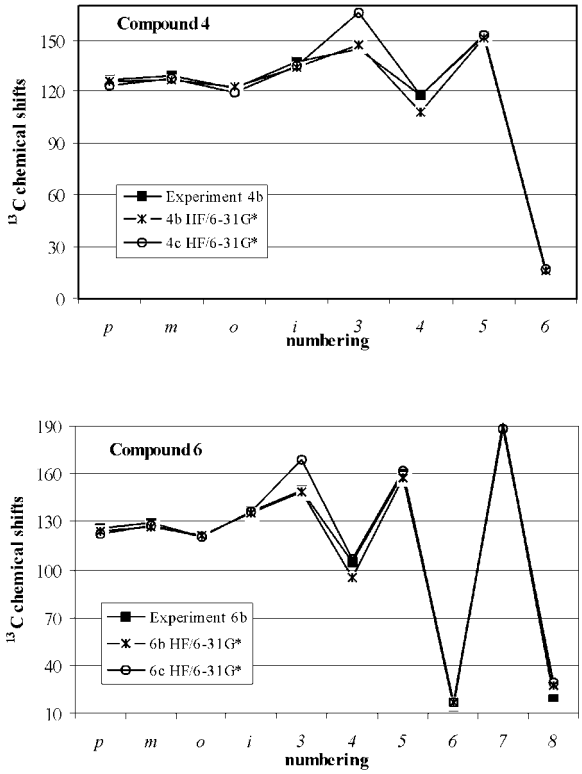


Figure 5. Experimental ^{13}C chemical shifts of the tautomers of **4** and **6** compared with the theoretically calculated shift values for fast NH/OH tautomeric interconversion

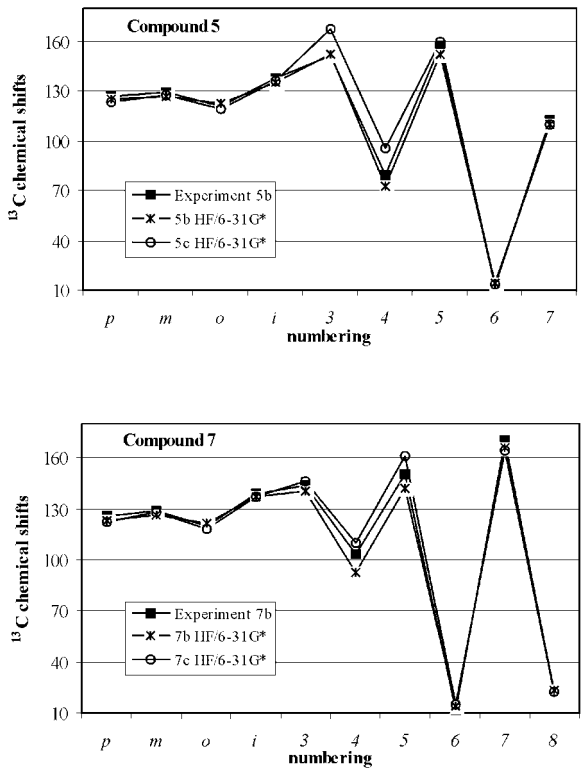


Figure 6. Experimental ^{13}C chemical shifts of the tautomers of **5** and **7** compared with the theoretically calculated shift values for fast NH/OH tautomeric interconversion

both positioned to lower field with respect to their counterparts in the NH/OH tautomers, which is correctly calculated at all levels of theory and within each of the various methods there is no overlap. The situation becomes problematic in the case of the NH/OH tautomers, as the chemical shifts of C-3 are very similar in the two tautomers; however, the correct order of C-4 in the two tautomers (to lower field in the NH tautomer) was correctly predicted in the theoretical analysis. Finally, the chemical shift of C-5 in the two tautomers (also to lower field in the NH tautomer) is also correctly calculated at all levels of theory. This latter result was most encouraging for calculating the ^{13}C NMR spectra of the tautomers of the other pyrazolinones **2**–**7** and in attempting to use the chemical shifts for estimating the position of the NH/OH

Copyright © 2001 John Wiley & Sons, Ltd.

equilibrium, since it was fast on the NMR time scale for all of the compounds **1–7**.

One disappointing result was the lack of improvement in accuracy for the ^{13}C chemical shifts of the OH tautomer **1b** if either the solvent or other intermolecular interactions were included in the calculations. Theoretically, this simulation stabilized the OH tautomer with respect to the CH and NH tautomers decisively and, for the first time, reproduced the tautomerism of **1–7** correctly (*vide supra*). Evidently, more advanced levels of theory, at least for the case of calculating ^{13}C chemical shifts, do not necessarily improve the quality of the result; this observation has been made previously when employing calculated ^{13}C chemical shifts for other phenomena (rotational twist, intramolecular hydrogen bonding) that are also fast on the NMR time scale.[35,36]

The agreement between the observed and the calculated shifts for the CH tautomers of **1–3** is excellent, and since the assignment is unequivocal the shifts are not represented in Fig. 4. For **1** (and also **2**) all three tautomers have been found in solution and the ^{13}C chemical shifts assigned; the agreement with the calculated results is satisfactory. For **2**, the calculated chemical shifts for the OH form were shown to deviate significantly from the experimental shifts; the chemical shifts for the NH form, however, were found to be in excellent agreement with the experimental shifts. For **3**, in addition to the CH tautomer, the NH tautomer has also been identified by ^{1}H NMR and IR spectroscopy to be present in $CDCl_3$ solution.[37,38] The observed ^{13}C chemical shifts, however, are in much better agreement with the chemical shifts calculated for the OH tautomer, and it may be concluded that for **3** also, as for all the other pyrazolin-5-ones substituted with a polar substituent in position 4, it is the OH tautomer that is the preferred second tautomer after the CH form.

Figure 5 depicts the observed and calculated shifts for **4** and **6**. In these two compounds, there are strong intramolecular hydrogen bonds involved that confer overwhelming predominance to the OH tautomer (*vide supra*). The agreement between experimental and theoretically calculated ^{13}C chemical shifts is good, in particular for C-3. However, since the experimental ^{13}C chemical shifts of the pyrazolin-5-one carbon atoms lie in between the calculated values obtained for the OH and the NH tautomer, a significant though minor proportion of the NH tautomer[27] can be inferred.

Finally, in Fig. 6 the experimental and theoretically calculated ^{13}C chemical shifts for **5** and **7** are compared. As for **4** and **6**, the experimental ^{13}C chemical shifts lie in between the calculated values for the NH and OH tautomers, and it can be concluded that fast exchange in the OH/NH tautomeric equilibria, which is again strongly biased towards the OH tautomer, is in effect. The strong bias is based on the much closer alignment of the experimental chemical shifts to the calculated chemical shifts for the OH tautomer. Equilibrium constants can obviously be calculated from these results, but the margin of error in these measurements at this stage does not warrant such evaluation.

Conclusions

It is possible to calculate correctly the position of the tautomeric equilibria of 4-substituted 1-phenyl-3-methyl-pyrazolin-5-ones employing *ab initio* methods. Considering either the effect of the solvent or intermolecular interactions between the tautomers themselves or with DMSO (as the solvent) improves the results considerably. From global minimum structures of the tautomers obtained by application of the GIAO perturbation theory, the ^{13}C NMR spectra of the tautomers could also be sufficiently calculated and compared with the experimentally obtained chemical shift values. The ^{13}C chemical shifts of the CH tautomers, observable in the ^{13}C NMR spectra, were calculated and found to be in excellent agreement with the experimental chemical shifts. For the tautomeric equilibria between the OH and NH tautomers, which is fast on the NMR time scale, only weighted averages of the ^{13}C chemical shifts for the two participating tautomers can be measured. For the non-substituted, 4-methyl- and 4-bromo-1-phenyl-3-methyl-pyrazolin-5-ones (**1–3**), the experimental tautomeric equilibria could be readily confirmed. For the 1-phenyl-3-methyl-pyrazolin-5-ones substituted with polar substituents in position 4 (**4–7**) the preferred OH tautomers could also be readily identified; however, owing to the inherent margin of error, minor proportions of the NH tautomer contributing to the equilibrium cannot be excluded.

EXPERIMENTAL

Total molecular energies of the tautomers were calculated using *ab initio* theory by employing the GAUSSIAN 98/94 series of programs.[31] Different levels of theory were applied, namely HF/6-31G*, HF/6-31G**, HF/6-311G**, HF/6-311+G**[23] and MP2/6-31G**,[24] together with DFT at level B3LYP/6-311+G**[25] (these latter two were used to account for the effect of electron correlation). The NMR chemical shifts were calculated using the GIAO method[39] as the difference of the carbon chemical shifts from a reference compound. The GIAO method is implemented in the GAUSSIAN 98/94 series of programs.[31] The ^{13}C chemical shifts of the tautomers of **1–7** were calculated with the 6-31G** basis set at the HF level of theory. For valid comparison, the chemical shift of the reference compound (tetramethyl silane) was carried out at the same level of theory as the tautomers. The quantum-chemical calculations were processed on SGI OCTANE (2 × R 12000) and SGI ORIGIN (32 × R 12/10000) computers.

Copyright © 2001 John Wiley & Sons, Ltd.

REFERENCES

1. Attanasi, OA, de Crescentini L, Filippone P, Foresti E, Galeazzi R, Ghiviriga I, Katritzky AR. *Tetrahedron* 1997; **53**: 5617.
2. Guard JAM, Steel PJ. *Aust. J. Chem.* 1994; **47**: 1453.
3. Olivieri AC, Sanz D, Claramunt RM, Elguero J. *J. Chem. Soc. Perkin Trans. 2* 1993; 1597.
4. Kumar D, Singh SP, Martinez A, Fruchier A, Elguero J, Martinez-Ripoll M, Carrio JS, Virgili A. *Tetrahedron* 1995; **51**: 4891.
5. Fabian WMF. *Z. Naturforsch. Teil A* 1990; **45**: 1328.
6. Tschmutova G, Ahlbrecht H. *Z. Naturforsch. Teil B* 1997; **52**: 535.
7. Katritzky AR, Karelson MM, Harris PA. *Heterocycles* 1991; **32**: 329.
8. Luque FJ, Lopez-Bes JM, Cemeli J, Aroztegui M. Orozco M. *Theor. Chem. Acc.* 1997; **96**: 105.
9. Cao M, Teppen BJ, Miller DM, Pranata J, Schäfer L. *J. Phys. Chem.* 1994; **98**: 11353.
10. Parchment OG, Green DVS, Taylor PJ, Hillier IH. *J. Am. Chem. Soc.* 1993; **115**: 2352.
11. Mo O, Yanez M, Llamas-Saiz AL, Foces-Foces C, Elguero J. *Tetrahedron* 1995; **51**: 7045.
12. Foces-Foces C, Llamas-Saiz AL, Menendez M, Jagerovic N, Elguero J. *J. Phys. Org. Chem.* 1997; **10**: 637.
13. Infantes L, Foces-Foces C, Claramunt RM, Lopez C, Elguero J. *J. Mol. Struct.* 1998; **447**: 71.
14. Elguero J, Marzin C, Katritzky AR, Linda P. *The Tautomerism of Heterocycles*. Academic Press: New York, 1976.
15. Elguero J. In *Comprehensive Heterocyclic Chemistry*, vol. 5. Pergamon Press: Oxford, 1984; 167.
16. Elguero J. In *Comprehensive Heterocyclic Chemistry II*, vol. 3. Pergamon Press: New York, 1996; 1.
17. Feeney J, Newman GA, Pauwels PJS. *J. Chem. Soc. C* 1970; 1842.
18. Hawkes GE, Randall EW, Elguero J, Marzin CJ. *J. Chem. Soc. Perkin Trans. 2* 1977; 1024.
19. Zeigan D, Kleinpeter E, Wilde H, Mann G. *J. Prakt. Chem.* 1981; **323**: 188.
20. Foces-Foces C, Fontenas C, Elguero J, Sobrados I. *An. Quim. Int. Ed.* 1997; **93**: 219.
21. Dardonville C, Elguero J, Rozas I, Fernandez-Castano C, Foces-Foces C, Sobrados I. *New J. Chem.* 1998; 1421.
22. Yranzo GI, Moyano EL, Rozas I, Dardonville C, Elguero J. *J. Chem. Soc. Perkin Trans. 2* 1999; 211.
23. Hehre WJ, Radom L, Schleyer PvR, Pople JA. In *Ab Initio Molecular Orbital Theory*. Wiley & Sons: New York, 1986.
24. Møller C, Plesset MS. *Phys. Rev.* 1934; **46**: 618.
25. Becke AD. *J. Chem. Phys.* 1993; **98**: 1372.
26. Kleinpeter E, Heydenreich M. Unpublished results.
27. Holzer W, Mereiter K, Plagens B. *Heterocycles* 1999; **50**: 799.
28. Begtrup M. *Acta Chem. Scand. Ser. B* 1974; **28**: 61.
29. Karelson MM, Katritzky AR, Szafran M, Zerner MC. *J. Org. Chem.* 1989; **54**: 6030.
30. Karelson MM, Katritzky AR, Szafran M, Zerner MC. *J. Chem. Soc. Perkin Trans. 2* 1990; 195.
31. Frisch MJ, Trucks GW, Schlegel HB, Gill PMW, Johnson BG, Robb MA, Cheeseman JR, Keith T, Petersson GA, Montgomery JA, Raghavachari K, Al-Laham MA, Zakrzewski VG, Ortiz JV, Foresman JB, Cioslowski J, Stefanow BB, Nanayakkara A, Challacombe M, Peng CY, Ayala PY, Chen W, Wong MW, Andres JL, Replogle ES, Gomperts R, Martin RL, Fox DJ, Binkley JS, Defrees DJ, Baker J, Stewart JJP, Head-Gordon M, Gonzales C, Pople JA. GAUSSIAN 94, Revision B.1. Gaussian: Pittsburgh, PA, 1995.
32. De Paz JLG, Elguero J, Foces-Foces C, Llamas-Saiz AL, Aguilar-Parrilla F, Klein O, Limbach HH. *J. Chem. Soc. Perkin Trans. 2* 1997; 101.
33. Claramunt RM, Alkorta I, Elguero J. *Heterocycles* 1999; **51**: 355.
34. Lopez C, Claramunt RM, Alkorta I, Elguero J. *Spectroscopy* 2000; **14**: 121.
35. Kleinpeter E, Hilfert L, Koch A. *J. Phys. Org. Chem.* 1999; **12**: 725.
36. Kleinpeter E, Hilfert L, Koch A. *J. Phys. Org. Chem.* 2000; **13**: 473.
37. Newman GA, Pauwels PJS. *Tetrahedron* 1969; **25**: 4605.
38. Dorn H. *J. Prakt. Chem.* 1973; **315**: 382.
39. Ditchfield R. *Mol. Phys.* 1974; **27**: 789.

Copyright © 2001 John Wiley & Sons, Ltd.