MAGNETIC RESONANCE IN CHEMISTRY, VOL. 29, 1147–1151 (1991)

Studies of Tautomerism and Protonation in 2-Aryl-1*H*-imidazo[1,2-*a*]imidazole Derivatives Using ^{1}H and ^{13}C NMR

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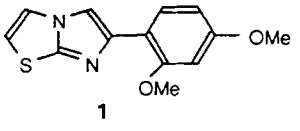
The tautomerism and protonation of the putative inotropic 2-(2′,4′-dimethoxy)phenyl-1*H*-imidazo[1,2-*a*]imidazole (2) has been studied in several solvents by comparing its ^{1}H and ^{13}C chemical shifts with those of its 1- and 7-methyl derivatives 3 and 4, respectively, and acid salts. Tautomer and rotamer populations were also estimated from measurements of proton relaxation rates and NOE effects. Heterocycle 2 exists predominantly as the 1*H*-tautomer in $CDCl_3$, but as the 7*H*-tautomer in DMSO-d_6 and methanol-d_4–D_2O solutions. In $CDCl_3$ solution, 2 appears to exist with the N-1-H and 2′-OMe groups adjacent, but in DMSO-d_6 the conformation is the rotated form with N-7-H and H-6′ adjacent; 3 exists as a mixture of rotamers in $CDCl_3$ and in DMSO-d_6 whereas 4 is in the form with the N-7-Me and H-6′ adjacent in both solvents. The observed conformational preferences have been compared with the results of semi-empirical molecular orbital calculations and found to be in broad agreement. Protonation of 2 occurs mainly at N-1 in DMSO-d_6 and at N-7 in $CDCl_3$, as expected from observed tautomeric ratios in the free base.

KEY WORDS Protonation Tautomerism NMR Imidazo[1,2-*a*]imidazole

INTRODUCTION

As part of a comprehensive study[1] of the structure–activity relationships and physicochemical properties of cardiotonic heterocycles, we have recently reported[2] the synthesis and pharmacological properties of sulmazole analogues **1** and **2**.



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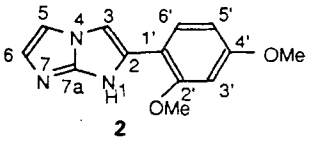

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Interestingly, whereas **1** displayed inotropic activity, the 1*H*-imidazo[1,2-*a*]imidazole **2** proved to be devoid of such activity. One possible explanation[2] requires that **2** exists predominantly as the inactive 1*H*-tautomer at the inotropic receptor site. We have previously characterized the tautomeric and protonation behaviour of a wide range of heterocycles,[3–5] and in an attempt to support or disprove this hypothesis we have investigated the tautomerism of **2** in solution and its protonation characteristics. To aid this study, we have also prepared the 1- and 7- methyl derivatives, **3** and **4**, confirmed their structures through the use of NMR and investigated the effect of protonation on their ^{1}H and ^{13}C NMR spectra. To facilitate NMR comparisons, the same numbering system has been employed for **2**–**4**. For **4**, the IUPAC notation is given in parentheses.

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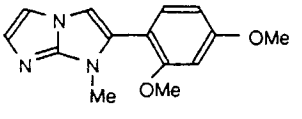

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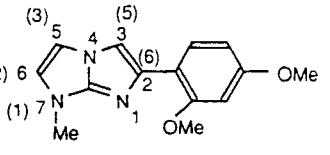

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EXPERIMENTAL

The synthesis of **1** and **2** has been discussed previously[2] and methods used for the preparation of **3** and **4** are described below. The structures of isomers **3** and **4** were confirmed through the use of ^{1}H NOE experiments.

^{1}H and ^{13}C NMR spectra were acquired at 30 °C on a Bruker AM-200 spectrometer operating at 200.13 MHz for ^{1}H and 50.2 MHz for ^{13}C. The chemical shifts were referenced to internal TMS (0.0 ppm for ^{1}H and ^{13}C). Typical parameters were as follows: for ^{1}H, tip angle 45°; spectral width 4000 Hz, 32K time domain points, 0.1 Hz line broadening; and for ^{13}C, tip angle 45°, spectral width 10000 Hz, 32K time domain points, zero-filled to 64 K before transformation, 1 Hz line broadening.

The two-dimensional ^{1}H–^{13}C heteronuclear correlation and NOE experiments were carried out using the standard Bruker microprograms. ^{1}H relaxation rates were measured using the standard inversion–recovery method. Typical acquisition and processing parameters for the heteronuclear correlations were 2K time domain points, 64 t_1 increments, zero-filling to 1K in the F_1

0749–1581/91/111147–05 $05.00

Received 6 June 1991
Accepted (revised) 23 July 1991

dimension, Gaussian weighting of the data in both domains, delay of 2.94 ms to cause correlations due to the one-bond J(CH) and a delay of 62.5 ms for correlations via long-range (mostly three-bond) J(CH). For the NOE studies the parameters were spectral width 4000 Hz, 32K time domain points and irradiation time 2 s. For the relaxation rate measurements the following parameters were used: relaxation delay 50 s, number of increments of delay 16 and other values as for the normal spectral acquisitions. Protonation of the free bases was achieved by the addition of small volumes of concentrated hydrochloric acid.

Theoretical calculations were carried out on a CRAY X-MP computer using the semi-empirical molecular orbital method MOPAC[6] with the AM1 Hamiltonian and geometry optimization.

SYNTHESIS

2-(2′,4′-Dimethoxyphenyl)-1-methylimidazo [1,2-*a*]imidazole (3)

1-(2′,4′-Dimethoxyphenacyl)-6-(2,4-dimethoxyphenyl)-imidazo [1,2-*a*]imidazole[2] (A) (0.30 g), acetone (3 ml) and methyl iodide (1.5 ml) were stirred for 1h and then allowed to stand for 4 days in the dark. The volatiles were removed *in vacuo* and the residue was stirred and triturated in ethyl acetate to give 0.26 g (65%) of A methiodide. This unstable material was dissolved in acetic acid–water (3:1) (8 ml) and acid-washed zinc (0.60 g) was added. The mixture was stirred vigorously for 4 h, the excess of zinc filtered off and washed with acetic acid and the filtrate evaporated. The residual gum was treated with 5% hydrochloric acid, extracted twice with ethyl acetate and the aqueous layer made alkaline with aqueous sodium hydrogencarbonate. The resulting suspension was extracted (twice) with chloroform, the extracts were dried (Na_2SO_4) and evaporated and the residue was stirred with EDTA disodium salt (0.25 g) in water (5 ml). After 1 h, the mixture was heated on a steam-bath for 5 min and, after cooling, made alkaline with aqueous sodium hydrogencarbonate. Extraction with chloroform and evaporation of the dried extracts gave a gum (90 mg) which was purified by preparative thin-layer chromatography [silica gel, $CHCl_3$–MeOH (12:1)] to yield 42 mg (36%) of **3** as a light-tan solid with no sharp melting point (decomp.) m/z 257 (M^+); R_F 0.63 [silica gel, $CHCl_3$–MeOH (8:1)]. Analysis: found C 65.6, H 6.0, N 16.1; $C_{14}H_{15}N_3O_2$ requires C 65.4, H 5.9, N 16.3%.

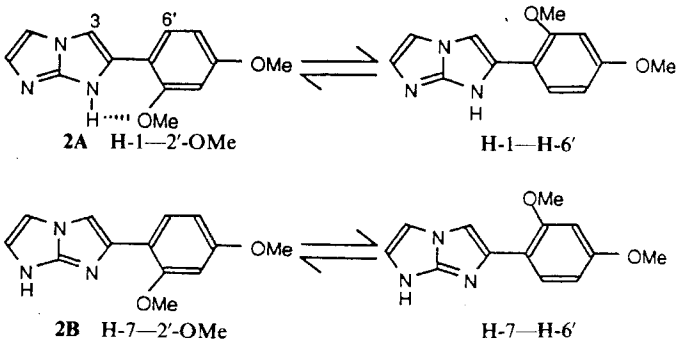
6-(2′,4′-Dimethoxyphenyl)-1-methylimidazo [1,2-*a*]imidazole (4)

To 2-amino-1-methylimidazole hydrochloride [7,8] (1.21 g, 8.0 mmol) in ethanol (20 ml) at 70 °C was added 2-bromo-2′,4′- dimethoxyacetophenone (2.08 g, 8.0 mmol). The mixture was stirred for 2 min, sodium hydrogencarbonate (1.34 g, 16.0 mmol) was added and heating and stirring were continued for 3 h. After cooling to room temperature, concentrated hydrochloric acid (2 ml) was added and the mixture stirred and heated at reflux for 5 h. The ethanol was evaporated, the residue neutralized with aqueous sodium hydrogencarbonate and then extracted (three times) with chloroform. The combined extracts were dried over Na_2SO_4 and evaporated to dryness, and the residue was chromatographed on silica gel. Elution with dichloromethane–ethanol (16:1) gave 0.92 g (44%) of **4**, m.p. 135–137 °C. m/z 257 (M^+); R_F 0.66 [silica gel, $CHCl_3$–MeOH (8:1)]. Analysis: found, C 65.2 H 6.0, N 16.0; $C_{14}H_{15}N_3O_2$ requires C 65.4, H 5.9, N 16.3%.

RESULTS AND DISCUSSION

The structure of **2** has been confirmed by detailed analysis of its NMR spectra and the resonances were asigned by standard methods including ^1H–^{13}C 2D correlations and ^1H–^1H NOEs, including NOEs observed from H-5 to H-3 and H-6, from 2′-OMe to H-3 and H-3′ and from 4′-OMe to H-5′ and H-3′. The ^1H chemical shifts are given in Table 1 and the ^{13}C shifts with some characteristic coupling constants are given in Table 2. In addition, we have characterized the N-1-Me (**3**) and N-7-Me (**4**) derivatives. The assignment of these structures was based on ^1H–^1H NOEs.

Compound **2** can exist as either the N-1-H tautomer **2A** or the N-7-H tautomer **2B**. Further, the 2-aryl ring can adopt a variety of rotational conformations, two of which are designated as shown.



2A H-1—2′-OMe H-1—H-6′

2B H-7—2′-OMe H-7—H-6′

Examination of the ^{13}C chemical shifts of **3** and **4** shows that C-2, C-6, C-7a and C-1′ are all good indicators for predicting the tautomer proportions of **2**. This conclusion assumes that substitution of N-H by N-Me has only a very small effect on the ^{13}C chemical shifts, and this assumption has been confirmed previously[5] in several closely related heterocycles.

Interpolating from differences in ^{13}C chemical shifts between **3** and **4**, the ^{13}C shifts of **2** in DMSO-d_6 solution give the calculated proportions of the N-7-H tautomer to be about 84 ± 16% of **2B**. We also measured the NMR spectra of **2**–**4** in $CDCl_3$ and the results are also given in Tables 1 and 2. Thus in $CDCl_3$ solution one can calculate the proportions of the N-7-H tautomer in the same fashion as above to give a proportion of **2B** of 17 ± 14%. In DMSO-d_6 solution both the C-2′ and C-6′ shifts also predict about 100% **2B**, in agreement with the other values. In $CDCl_3$ solutions, however, the

Table 1. ^{1}H NMR chemical shifts for 2–4

Compound	3	5	6	3′	5′	6′	2′-OMe	4′-OMe	NH	NMe
(2) base DMSO-d_6	7.52	7.16	6.98	6.62	6.58	7.88	3.89	3.78	11.2	—
(2) salt[a] DMSO-d_6	7.78	7.61	7.44	6.74	6.62	7.85	3.93	3.83	13.7	—
(2) base $CDCl_3$	7.35	6.97	6.97	6.58	6.47	7.61	3.95	3.82	8.11	—
(2) base CD_3OD	7.49	7.10	6.93	6.61	6.58	7.66	3.91	3.81	—	—
(2) base CD_3CN	7.51	7.06	6.93	6.61	6.55	7.79	3.91	3.81	—	—
(2) base CD_3OD–D_2O	7.51	7.13	6.98	6.63	6.63	7.68	3.91	3.83	—	—
(3) base DMSO-d_6	7.19	7.18	6.92	6.72	6.64	7.25	3.83	3.81	—	3.31
(3) base $CDCl_3$	6.87	7.09	7.03	6.56	6.55	7.20	3.86	3.81	—	3.46
(3) base CD_3OD–D_2O	7.14	7.22	7.11	6.76	6.70	7.32	3.95	3.92	—	3.38
(4) base DMSO-d_6	7.54	7.19	7.03	6.60	6.58	8.04	3.90	3.78	—	3.59
(4) salt DMSO-d_6	7.79	7.54	7.37	6.64	6.62	7.66	3.88	3.80	—	3.78
(4) base $CDCl_3$	7.54	6.88	6.58	6.53	6.59	8.11	3.91	3.83	—	3.68
(4) base CD_3OD–D_2O	7.63	7.18	6.96	6.68	6.68	7.99	3.99	3.90	—	3.75

[a] Salt forms were generated from free bases by the addition of HCl.

Table 2. ^{13}C chemical shifts and coupling constants for 2–4

Compound	2	2	2	2	3	3	3	4	4	4	4
Base/salt[a]	Base	Salt	Base	Base	Base	Base	Base	Base	Salt	Base	Base
Solvent	DMSO-d_6	DMSO-d_6	CD_3OD–D_2O	$CDCl_3$	DMSO-d_6	$CDCl_3$	CD_3OD–D_2O	DMSO-d_6	DMSO-d_6	$CDCL_3$	CD_3OD–D_2O
C-2	135.6	130.1	132.9	133.1	129.9	130.3	132.6	138.9	131.0	140.3	140.0
C-3	103.9	106.1	101.4	103.5	103.0	102.8	104.5	104.9	107.3	105.4	106.8
C-5	105.2	108.8	106.8	105.1	105.6	105.6	107.3	104.5	109.5	104.6	106.1
C-6	120.6	120.0	123.9	124.0	130.0	130.5	128.6	120.7	124.2	119.9	121.8
C-7a	147.2	138.9	148.7	151.1	149.2	148.9	146.7	147.0	139.7	147.8	148.6
C-1′	115.6	109.3	115.3	114.0	109.9	110.7	109.7	117.0	109.2	117.5	117.9
C-2′	156.7	157.3	158.8	157.2	158.5	158.9	160.4	156.6	158.2	157.5	158.7
C-3′	98.5	99.0	99.7	99.1	98.7	98.7	99.5	98.3	99.3	98.8	99.5
C-4′	159.0	161.0	161.7	160.0	161.7	162.3	164.0	158.7	161.8	159.5	161.1
C-5′	105.1	105.7	106.2	105.1	105.2	104.6	106.2	104.9	106.5	104.9	106.0
C-6′	127.5	128.3	128.8	128.2	132.6	132.9	134.0	127.8	128.6	128.9	129.3
C-2′-OMe	55.4	55.9	55.9	55.5	55.5	55.4	55.9	55.3	56.6	55.5	55.8
C-4′-OMe	55.2	55.7	55.9	55.4	55.4	55.4	55.9	55.1	56.3	55.5	55.8
N-Me	—	—	—	—	29.7	30.0	30.4	31.7	34.2	32.5	32.4
^1J(C-3–H-3)	199.5	207.9		199.9	199.1	197.7		198.2	209.0	198.9	199.3
^1J(C-5–H-5)	197.3	199.6		194.6	194.6	193.7		199.6	207.5	197.5	199.3
^3J(C-5–H-3)	12.8	12.4		14.5	16.8	16.2		11.4	11.5	10.8	11.5
^1J(C-6–H-6)	190.5	205.6		188.5	185.4	186.6		192.7	201.4	191.2	194.1
^2J(C-6–H-5)	11.7	12.2		12.2	10.7	10.6		12.0	12.2	11.4	11.4
^1J(C-3′–H-3′)	157.8	159.9		157.2	160.0	160.0		157.8	154.1	156.3	157.4
^3J(C-3′–H-5′)	4.5	5.1		5.4	5.5	4.8		4.4	6.1	5.4	5.6
^1J(C-5′–H-5′)	161.3	163.2		161.7	158.7	162.0		161.2	164.0	160.9	161.6
^3J(C-5′–H-3′)	4.1	4.6		4.6	3.4	4.2		5.0	4.6	5.5	4.8
^1J(C-6′–H-6′)	160.0	167.6		159.5	161.0	160.1		160.4	158.7	160.3	159.5

[a] Salt forms were generated from free bases by the addition of HCl.

observed ^{13}C shifts of C-2′ and C-6′ now suggest 100% of **2B**, in disagreement with the predominance of **2A** predicted from the other shifts. One possible explanation of this discrepancy is that **3** and the 1*H*-tautomer of **2** as found in $CDCl_3$ exist in different conformations owing to rotation of the 2-aryl ring. We measured a number of NOEs for **3** in $CDCl_3$, including those from H-3 to H-6′ and from N-1-Me to H-6′, indicating that both ring conformers are significantly populated.* On the other hand, it is likely that one rotamer is populated for **2** in $CDCl_3$ because of a favourable hydrogen bond from the N-1-H to the OMe group, then the ^{13}C chemical shifts for C-2′ and C-6′ may be different.

There are negligible chemical shift differences for **3** between $CDCl_3$ and DMSO-d_6 solution, which leads to the conclusion that the conformation of **3** is similar in these two solvents, existing as a mixture in both. Indeed, ^{1}H–^{1}H NOE measurements on **3** in DMSO-d_6 also show interactions between H-3 and 2′-OMe and between the 2′-OMe and NMe group, indicating that both rotamers are significantly populated. Such a difference in rotamer populations induced by a replacement of an NH by an *N*-methyl moiety would not be surprising, as steric interactions between the methyl and 2′-OMe groups and the disruption of intramolecular hydrogen bonding between the NH and 2′-OMe group could easily account for such a difference.

* Although we restrict the discussion to only two planar conformations, it is recognized that on the NMR time scale these molecules are in a dynamic equilibrium and will adopt a range of conformations, some of which will be of low population. NMR will detect a population-weighted average of these conformations and hence the term 'conformation' used here can be taken as an abbreviated notation for this situation.

Table 3. Conformational and tautomeric preferences for 2–4

Compound	Solvent	Tautomer	Rotamers
2	$CDCl_3$	N-1-H	N-1-H/2′-OMe
2	DMSO-d_6	N-7-H	N-7-H/H-6′
3	$CDCl_3$		N-1-Me/2′-OMe
			N-1-Me/H-6′
3	DMSO-d_6		N-1-Me/2′-OMe
			N-1-Me/H-6′
4	$CDCl_3$		N-7-Me/H-6′
4	DMSO-d_6		N-7-Me/H-6′

Observations on **4** in DMSO-d_6 where NOEs are detected between H-3 and 2′-OMe but not between H-3 and H-6′ indicate that the N-7-Me—H-6′ conformer is the principal form. The similarity of ^{13}C chemical shifts in DMSO-d_6 between **2** and **4** then leads to the suggestion that **2**, which exists as the N-7-H form in DMSO-d_6, is also in the N-7-H—H-6′ form. In addition, the similarity of the ^{13}C shifts for **4** in $CDCl_3$ and DMSO-d_6 leads to the conclusion that **4** exists in the N-7-Me—H-6′ rotamer form in both solvents. These conclusions are summarized in Table 3.

We also measured the relaxation rates of individual protons in **2** in both DMSO-d_6 and $CDCl_3$ solutions, and these are given in Table 4. These provide additional evidence for a change in tautomeric proportions between the two solvents because the relative ratios will be indicative of dipolar relaxation contributions at the different proton sites. Some of the normalized ratios show significant deviations from unity and hence in $CDCl_3$ H-6 is relatively slowly relaxed because the preferred tautomer is now N-1-H, whereas in DMSO-d_6 the N-7-H proton increases the relaxation rate of H-6. However, H-6′ is relatively more efficiently relaxed in $CDCl_3$ solution, also indicating the presence of the N-1-H tautomer.

Relaxation rates were also measured for the protons in **3** and **4** in $CDCl_3$ and these are listed in Table 5. In general, the observations are in agreement with the tautomers and rotamers derived for the various molecules and solvent systems above. Thus, H-6′ relaxes fastest in **2**, and faster in **3** than **4**. In **2** H-6′ is adjacent to H-3, whereas in **3** H-3 is only adjacent for part of the time and for **4** H-6′ is not adjacent to any heterocyclic ring proton. H-3′ relaxes faster in the *N*-Me compounds **3** and **4** because the 2′-OMe group can exist at least partly in a bent-back conformation, confirmed by the lack of NOE observed from H-3 to 2′-OMe in **3**. The fact that H-6 and H-5 both relax fastest in **4** is explained by the nearness of the N-7-Me group. The relative relaxation rates of H-3 are neatly explained by the conformations derived above in that this nucleus relaxes fastest in **4** because of the proximity of the 2′-OMe group in the predominant form, the relaxation in **3** is next most efficient because for at least part of the time **3** is in the same conformation. Finally, in **2** the relaxation of H-3 is least efficient because the molecule exists mainly as the other rotamer, and H-6′ is less effective than a 2′-OMe group in enhancing the relaxation rate.

Table 4. ^1H relaxation rates (s^{-1}) for 2

	$CDCl_3$	DMSO-d_6	Ratio[a]
H-3	0.15	0.24	0.98
H-5	0.24	0.36	1.05
H-6	0.24	0.50	0.75
H-3′	0.42	0.86	0.77
H-5′	0.58	0.90	1.00
H-6′	0.66	0.81	1.28

[a] Ratio of rates in $CDCl_3$ and DMSO-d_6 and normalized to the ratio for H-5′, which is expected to be unaffected by changes in tautomeric or conformational proportions.

Table 5. ^1H relaxation rates for 2–4[a] relative to that of H-5′ in each case

	2	3	4
H-3	0.26	0.48	0.58
H-5	0.41	0.55	0.72
H-6	0.41	0.55	0.75
H-3′	0.72	1.00	1.17
H-5′	1.00	1.00	1.00
H-6′	1.14	0.86	0.81

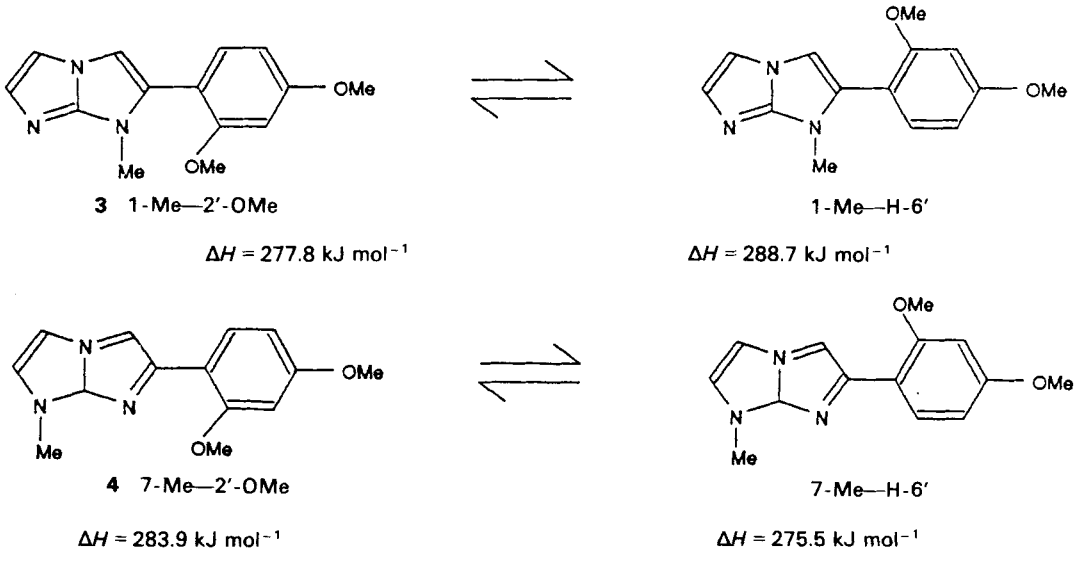
[a] $CDCl_3$ solution.

Inspection of the ^{13}C shifts of **2–4** in methanol–water solution (Table 2) indicates that the tautomer ratio demonstrates principally the presence of the N-7-H form, as in DMSO-d_6 solution. Interestingly, in methanol-d_4–D_2O solution H-3 exchanges slowly with deuterium, causing the ^1H resonance to be lost and the C-3 resonance to show ^{13}C–^2H coupling. A similar hydrogen–deuterium exchange at H-3 and H-5 has been observed[9] for the parent heterocycle, 1*H*-imidazo[1,2-*a*] imidazole.

An x-ray crystallographic study of **2** has shown it exists in the H-1–H-6′ form in the crystal.[2] Semi-empirical MO calculations predict the energies of the various species to be in the order N-1-H – H2′-OMe < N-1-H—H-6′ < N-7-H—H-6′ < N-7-H—2′-OMe. Although the N-1-H—2′-OMe rotamer (the form found in $CDCl_3$ solution) is of lowest energy, and the N-7-H—H-6′ form (as found in DMSO-d_6) is of higher energy, the difference in heat of formation (ΔH) between the two forms is small (16.5 kJ mol^{-1}). Hence, on the basis of these calculations, solvation effects would be expected to influence the distribution of tautomeric and rotameric species, and indeed such effects appear to be important given the solvent dependence of the NH chemical shift in **2** (Table 1).

Similar calculations were carried out for the two *N*-methyl isomers **3** and **4**. Thus, for the N-1-Me isomer (**3**) the difference in the heat of formation of the two rotamers is only 11 kJ mol^{-1} and consistent with the presence of both rotamers as seen in $CDCl_3$ solution. For the N-7-Me isomer (**4**), the calculations predict that the N-7-Me—H-6′ rotamer is the more stable and, indeed, this is the form seen in both $CDCl_3$ and DMSO-d_6.

The chemical shift changes observed on protonation of **2** in DMSO-d_6 indicate that this occurs at N-1, as



expected, and thus provide additional evidence of the base existing as the N-7-H tautomer. The site of protonation is deduced from the well known shielding effect at the adjacent carbon to the protonated nitrogen.[3–5] Hence for **2** in DMSO-d_6, shielding is observed at C-2 and C-7a but not at C-6. The protonation of **4**, the N-7-Me analogue,was also studied here for comparison and similar chemical shift effects are observed to those seen for **2**, i.e. shielding at C-2 and C-7a but not at C-6, showing that protonation is at N-1.

In summary, ^{1}H and ^{13}C chemical shift and ^{1}H relaxation data for **2–4** and their salts indicate that heterocycle **2** exists predominantly as the 1*H*-tautomer in $CDCl_3$ solution and as the 7-*H*-tautomer in DMSO-d_6 and methanol-d_4–D_2O. Further, proton relaxation time and NOE measurements in the above solvents have provided evidence to show that **2** exists mainly as the N-1-H—2'-OMe rotamer in $CDCl_3$ and as the N-7-H—H-6 rotamer in DMSO-d_6, that **3** exists as a mixture of rotamers in $CDCl_3$ and DMSO-d_6 and that **4** adopts the N-7-Me—H-6' conformer in both $CDCl_3$ and DMSO-d_6.

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