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CALORIMETRIC STUDY OF THE EFFECT OF *N*-METHYLATION IN AZOLES: LOSS OF AN ACTIVE CENTRE OF SOLVATION

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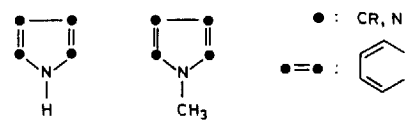
ABSTRACT

Using a series of equations connecting experimental and theoretical values, it is possible to discuss the origin of the *N*-methylation effect in azoles dissolved in water and dimethyl sulphoxide. The existence in the azoles studied of a linear relationship between the gas → solution transfer enthalpies and the charge on the pyrrole hydrogen atom demonstrated the fundamental importance of the loss of an active centre for solvation. For the imidazole–*N*-methylimidazole pair, the complete thermochemical cycle has been determined, allowing the apparent lack of an effect of *N*-methylation on the basicity in solution to be discussed.

INTRODUCTION

The effect of *N*-methylation on the acid–base properties of azoles in aqueous solution has been the subject of many studies.[1–5] Moreover, *N*-methylazoles are commonly used as models to study the annular tautomerism of azoles.[1–7] However, there is still much work to be done to understand completely the origin and importance of the *N*-methylation effect.



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In water, the replacement of an aromatic CH (benzene) by a methyl group (toluene), i.e. the *C*-methylation effect, has been studied calorimetrically by Gill *et al.*[8] The results obtained at 298·15 K for $\Delta H_t^{g \rightarrow H_2O}$ ($-7{\cdot}59 \pm 0{\cdot}01$ and $-8{\cdot}69 \pm 0{\cdot}01$ kcal mol^{-1}, respectively) show that the phenomenon is more exothermic for toluene by $-1{\cdot}1$ kcal mol^{-1}.

A similar behaviour is observed for pyridines when 4-methylpyridine ($\Delta H_t^{g \rightarrow H_2O} = -13{\cdot}2$ kcal mol^{-1})[9] and pyridine ($\Delta H_t^{g \rightarrow H_2O} = -11{\cdot}9$ kcal mol^{-1})[9] are compared. In this case, the *C*-methylation effect is slightly larger ($-1{\cdot}3$ kcal mol^{-1}), partly owing to an increase in the basicity of the nitrogen centre produced by the methyl substituent, which, in turn, increases the energy of the N:···H_2O bond.

In dimethyl sulphoxide (DMSO), the benzene–toluene pair behaves in a similar way as in water. Thus, the gas → DMSO transfer is more exothermic for toluene ($-8{\cdot}17$ kcal mol^{-1})[10] than for benzene ($-7{\cdot}34$ kcal mol^{-1});[10] hence $\delta\Delta H_t^{g \rightarrow DMSO} = -0{\cdot}83$ kcal mol^{-1}.

To summarize, all the available information shows that for aromatic and heteroaromatics compounds, both in water and in DMSO, the *C*-methylation effect amounts to ca 1 kcal mol^{-1}.

EXPERIMENTAL

Materials

Pyrrole was obtained from Aldrich. Imidazole and pyrazole were kindly supplied as pure samples by Dr Turrión. The samples were identical with those described in Ref. 11. *N*-Methylpyrrole, *N*-methylimidazole and *N*-methylpyrazole were prepared and purified according to literature procedures.[12] Their purity was determined by gel permeation and high-performance liquid chromatography. In all cases, the purity was higher than 99·8%. DMSO (Merck) was used without further purification, but before the experiment it was dried over 4 Å molecular sieves. Carbon dioxide-free water was produced with a Milli-Q filtration system (Millipore).

Calorimetric dissolution measurements

The enthalpy of solution of *N*-methylpyrrole in water was obtained by use of a vessel which fits a Thermometrics thermal activity monitor.[13] A spiral-wound thin-walled gold tube is suspended in the water-filled sample cup of an insertion vessel of the type described in Ref. 13. The sample is injected into the gold spiral through which water was pumped at a rate of 11 mm^3 s^{-1}. Calibrations were performed electrically and by dissolution of propan-1-ol in water at 298·15 K.

The enthalpies of solution of pyrrole, *N*-methylimidazole and *N*-methylpyrazole in water and DMSO were determined by using an LKB batch microcalorimeter equipped with a titration unit. The instrument was calibrated electrically and by means of neutralization of HCl with NaOH. The experiments were carried out by addition of 5·20 μl of sample to the reaction vessel which contained 6 ml of water or DMSO; 10–15 measurements were normally performed for each compound.

The enthalpies of solution of imidazole and pyrazole in water and DMSO were determined using an isoperibol calorimeter similar to that described previously.[14]

Calorimetric vaporization measurements

For methylpyrrole and methylimidazole, the enthalpy of vaporization measurements were

performed by use of a calorimeter of the type described in Ref. 15. Six measurements were made for each compound.

Uncertainties in values reported in this paper are twice the overall standard deviation of the mean.

RESULTS

The data used in the following discussion are those in Table 1. First, we shall examine the validity of the model chosen to discuss the *N*-methylation effect, i.e. the comparison between an azole and its *N*-methyl derivative in the simplest case, that of pyrrole.

Pyrrole N-methylpyrrole

Considering the $\Delta H_f^{g \rightarrow H_2O}$ values for these compounds, it can be seen that the introduction of a methyl group on the nitrogen produces a decrease in exothermicity. This loss amounts to $+0{\cdot}71$ kcal mol^{-1} for the gas → water transfer and $+3{\cdot}47$ kcal mol^{-1} for the gas → DMSO transfer. These values are very different from those reported in Ref. 8 for the benzene–toluene pair ($-1{\cdot}1$ and $-0{\cdot}83$ kcal mol^{-1}, respectively). As we shall discuss in detail later, the explanation lies in the fact that an azole NH group (pyrrole hydrogen atom) is much more acidic than an aromatic CH group. Hence the replacement of a hydrogen with a methyl group results, in the case of azoles, in a loss of an active centre for solvation with a concomitant loss of enthalpy of solvation.

From ΔH_{sol}^0 values for pyrrole and *N*-methylpyrrole in pyridine[16] and the corresponding ΔH_{vap}^0 values in Table 1, values of $-12{\cdot}81$ and $-9{\cdot}53$ kcal mol^{-1} are obtained for ΔH_{solv}^0 in pyridine for pyrrole and *N*-methylpyrrole, respectively.

The comparision of these values with those corresponding to the gas → water transfer (Table 1) shows that with *N*-methylpyrrole the effect of the solvent on the basicity increase is almost negligible, whereas with pyrrole the overstabilization in pyridine reaches 2.3 kcal mol^{-1}.

To summarize, for pyrrole the *N*-methylation effect is $0{\cdot}71$ kcal mol^{-1} in water, $2{\cdot}3$ kcal mol^{-1} in pyridine and $3{\cdot}47$ kcal mol^{-1} in DMSO. These parallel the hydrogen-bond basicities of the solvents as measured by their β values, viz. $0{\cdot}18$, $0{\cdot}64$ and $0{\cdot}76$, respectively.[17]

Table 1. Enthalpies of solution, ΔH_{sol}^0, enthalpies of vaporization of sublimation, $\Delta H_{v/sub}^0$, and enthalpies of solvation, $\Delta H_f^{g \rightarrow sol}$, for some azoles at 298·15 K (values in kcal mol^{-1})

Compound	$\Delta H_{sol}^0(H_2O)$	ΔH_{sol}^0(DMSO)	$\Delta H_{v/sub}^0$	$\Delta H_f^{g \rightarrow H_2O}$	$\Delta H_f^{g \rightarrow DMSO}$
Pyrrole	$0{\cdot}65 \pm 0{\cdot}04$	$-2{\cdot}23 \pm 0{\cdot}06$	$10{\cdot}84 \pm 0{\cdot}02$[a]	$-10{\cdot}19 \pm 0{\cdot}06$	$-13{\cdot}07 \pm 0{\cdot}08$
1-Methylpyrrole	$0{\cdot}25 \pm 0{\cdot}03$	$0{\cdot}13 \pm 0{\cdot}04$	$9{\cdot}73 \pm 0{\cdot}07$	$-9{\cdot}48 \pm 0{\cdot}10$	$-9{\cdot}60 \pm 0{\cdot}11$
Imidazole	$3{\cdot}09 \pm 0{\cdot}01$[b]	$2{\cdot}58 \pm 0{\cdot}02$	$19{\cdot}86 \pm 0{\cdot}05$[c]	$-16{\cdot}77 \pm 0{\cdot}06$	$-17{\cdot}28 \pm 0{\cdot}07$
1-Methylimidazole	$-2{\cdot}33 \pm 0{\cdot}3$	$-0{\cdot}04 \pm 0{\cdot}03$	$13{\cdot}06 \pm 0{\cdot}11$	$-15{\cdot}39 \pm 0{\cdot}14$	$-13{\cdot}10 \pm 0{\cdot}14$
Pyrazole	$3{\cdot}73 \pm 0{\cdot}04$	$2{\cdot}08 \pm 0{\cdot}02$	$17{\cdot}68 \pm 0{\cdot}05$[c]	$-13{\cdot}95 \pm 0{\cdot}09$	$-15{\cdot}60 \pm 0{\cdot}07$
1-Methylpyrazole	$-1{\cdot}47 \pm 0{\cdot}06$	$-0{\cdot}16 \pm 0{\cdot}07$	$10{\cdot}00 \pm 0{\cdot}04$[d]	$-11{\cdot}47 \pm 0{\cdot}10$	$-10{\cdot}16 \pm 0{\cdot}11$

The values given for ΔH_{sol}^0 in water for pyrrole and methylimidazole are in good agreement with those in Ref. 16, and agree well with the values in Ref. 19 for ΔH_{sol}^0 in water and DMSO for imidazole and methylimidazole.

[a] see Ref. 20.

[b] see Ref. 24.

[c] see Ref. 11.

[d] see From the relationship existing between ΔH_v and T_{bp} in ternary amines and *N*-methylazoles (see Figure 1).

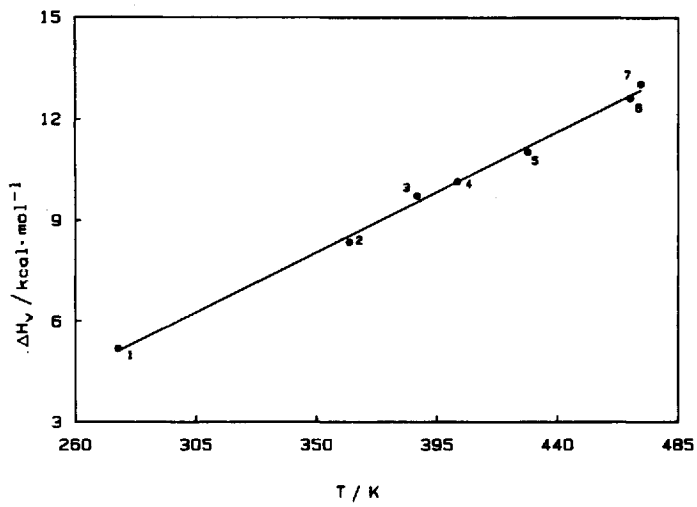


Figure 1. Relationship between ΔH_v^0 and T_{bp}. 1 = Trimethylamine; 2 = triethylamine; 3 = *N*-methylpyrrole; 4 = *N*-ethylpyrrole; 5 = tripropylamine; 6 = *N*,*N*-dimethylaniline; 7 = *N*-methylimidazole. ΔH_v^0 values for compounds 1, 2, 5 (Ref. 21), 4 (Ref. 23) and 6 (Ref. 22) are from literature.

Along these lines, we shall now analyse the remaining data in Table 1. The *N*-methylation effect in water and DMSO amounts to, in addition to 0·71 and 3·47 kcal mol^{-1} for pyrrole, 1·38 and 4·18 kcal mol^{-1} for imidazole and 2·48 and 5·44 kcal mol^{-1} for pyrazole, respectively. Hence the effect is very sensitive to the nature of the azole and clearly more intense in DMSO than in water.

Hydrogen-bond interactions between the NH of the azole and the solvent together with hydrophobic and solvophobic interactions of the methyl group are mainly responsible for this effect. The latter should be constant in each solvent. Since for each azole–methylazole pair the differences in their dipolar moments and molar volumes are negligible, the interactions due to the polarity or the cavity effect are cancelled when considering the $\delta\Delta H_t^{g \rightarrow sol}$ term in the equation.

$$\delta\Delta H_t^{g \rightarrow sol} = \Delta H_t^{g \rightarrow sol}(N\text{-Me-azole}) - \Delta H_t^{g \rightarrow sol}(\text{azole}) \quad (1)$$

We should expect these transfer enthalpies differences, $\delta\Delta H_t^{g \rightarrow sol}$, to be higher when the azoles have a more positive charge, $1 - q_H$, on their pyrrole hydrogen. The values of $1 - q_H$ for pyrrole, imidazole and pyrazole and the transfer enthalpy differences for each azole in water and DMSO are given in Table 2.

In Figure 2, values of $\delta\Delta H_t^{g \rightarrow sol}$ are plotted against the net charge on the pyrrolic hydrogen $(1 - q_H)$, calculated at the 6–31 G//6–31 G level.[18] A linear relationship is obtained for the

Table 2. Pyrrolic hydrogen net positive charge $(1 - q_H)$ calculated at the 6–31 G//6–31 G level, and loss of exothermicity in water and DMSO due to the *N*-methylation effect, $\delta\Delta H_t^{g \rightarrow H_2O}$ and $\delta\Delta H_t^{g \rightarrow DMSO}$

Compound	$1 - q_H$	$\delta\Delta H_t^{g \rightarrow H_2O}$ (kcal mol^{-1})	$\delta\Delta H_t^{g \rightarrow DMSO}$ (kcal mol^{-1})
Pyrrole	0·380	0·71	3·47
Imidazole	0·392	1·38	4·18
Pyrazole	0·405	2·48	5·44

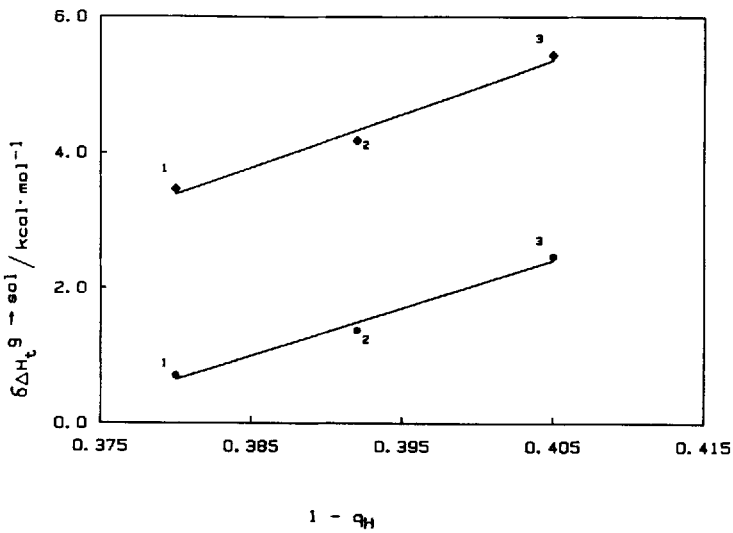
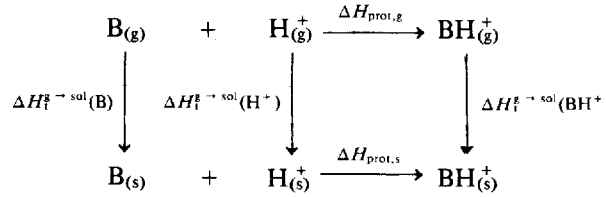


Figure 2. $\delta\Delta H_t^{g \rightarrow sol}$ in water (•) and in DMSO (◆) plotted against the net positive charge ($1 - q_H$). 1 = Pyrrole; 2 = imidazole; 3 = pyrazole

three azoles. The behaviour in the two solvents (water and DMSO) is parallel, the effect of *N*-methylation being more intense in DMSO than in water, which was to be expected as the hydrogen-bond basicity of DMSO ($\beta = 0{\cdot}76$)[17] is higher than that of water ($\beta = 0{\cdot}18$).[17]

The usually accepted idea[3,4] that *N*-methylation does not appreciably affect the aqueous basicity of an azole (see Table 3) can now be verified. This is possible since all the necessary data are known for the imidazole–*N*-methylimidazole pair: gas-phase basicities,[6] $\Delta H_{prot,s}$ (Table 3) and ΔH_{vap} or ΔH_{sub} (Table 1). From these data and using a thermochemical cycle, it is possible to calculate the gas → solution transfer enthalpies of neutral and protonated forms:



where (g) means gas and (s) solution. The knowledge of all these quantities enables us to discuss in detail the effect of *N*-methylation on the basicity of imidazole.

Table 3. pK_a and ΔH of protonation of imidazole and *N*-methylimidazole, in water and DMSO at 25 °C

Parameter	Imidazole	*N*-Methylimidazole
pK_a(H_2O)[a]	7·11 ± 0·02	7·25 ± 0·01
pK_a(DMSO)[b]	6·26 ± 0·06	6·15 ± 0·01
$\Delta H_{prot,H_2O}$(kcal mol^{-1})[a]	−8·82 ± 0·05	−8·08 ± 0·07
$\Delta H_{prot,DMSO}$(kcal mol^{-1})[b]	−10·13 ± 0·10	−9·27 ± 0·17

[a] Ref. 6.
[b] Ref. 19.

Examination of the results in Table 4 leads to the following conclusions:

i. The similarity of imidazole and *N*-methylimidazole with regard to solution basicity is a consequence of the cancellation in the thermochemical cycle of terms that are completely different in nature [see equation (2) and Table 4].

$$\Delta H_{\text{prot,s}} = \Delta H_{\text{prot,g}} + \Delta H_{\text{t}}^{\text{g}\rightarrow\text{sol}}(\text{BH}^+) - \Delta H_{\text{t}}^{\text{g}\rightarrow\text{sol}}(\text{B}) - \Delta H_{\text{t}}^{\text{g}\rightarrow\text{sol}}(\text{H}^+) \quad (2)$$

The first term, $\Delta H_{\text{prot,g}}$, refers to the intrinsic basicity, i.e. the gas-phase basicity. We have previously shown[6] that the idea that *N*-methylation does not affect the basicity is not correct, e.g. *N*-methylimidazole is 3·4 kcal mol^{-1} more basic than imidazole.

In aqueous solution, the $\Delta H_{\text{t}}^{\text{g}\rightarrow\text{H}_2\text{O}}(\text{B})$ term also increases comparatively the basicity of *N*-methylimidazole by 1·43 kcal mol^{-1} whereas the $\Delta H_{\text{t}}^{\text{g}\rightarrow\text{H}_2\text{O}}(\text{BH}^+)$ term is responsible for the cancellation of the aforementioned contributions.

In DMSO solution, again the $\Delta H_{\text{t}}^{\text{g}\rightarrow\text{DMSO}}(\text{B})$ term favours the basicity of the *N*-methyl derivative, but in this solvent to an even greater extent (4·18 kcal mol^{-1}). Since the $\Delta H_{\text{t}}^{\text{g}\rightarrow\text{DMSO}}(\text{BH}^+)$ term also undergoes a considerable increase (Table 4), the three effects are cancelled.

Accordingly, both in water and in DMSO, the relative insensitivity of the imidazole pK_a value to *N*-methylation (Table 3) hides the fact that two effects have increased (intrinsic basicity and solvation of the neutral form) but a third (solvation of the conjugated acid) has decreased, overcompensating the balance (see $\Delta H_{\text{prot,s}}$, Table 3).

Direct comparision between pK_a values (related to ΔG) and ΔH values is justified in this case because there is a linear relationship between ΔG^0_{prot} and ΔH^0_{prot} for azoles, both in aqueous solution[7] and in DMSO.[19]

ii. Since imidazole and *N*-methylimidazole have similar polarities, the analysis of the solvation effects (in water and in DMSO) casts new light on the nature of the *N*-methylation effect. To a large extent, the discriminating action of the solvent lies in the number of active acid centres for solvation, the $\delta\Delta H_{\text{t}}^{\text{g}\rightarrow\text{s}}(\text{BH}^+)$ differences being larger in the case of the most basic solvent (DMSO).

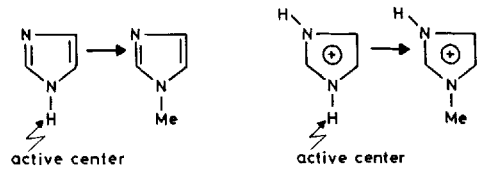


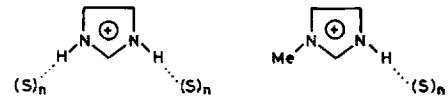
Table 4. Values of the thermochemical cycle [Eqn (2)] for imidazole and *N*-methylimidazole (values in kcal mol^{-1})

Parameter	Imidazole	*N*-Methylimidazole
$\Delta H_{\text{prot,g}}$[a]	−233·6	−227·0
$\Delta H_{\text{t}}^{\text{g}\rightarrow\text{H}_2\text{O}}(\text{BH}^+)$	−71·99	−66·47
$\Delta H_{\text{t}}^{\text{g}\rightarrow\text{H}_2\text{O}}(\text{B})$[b]	−16·77	−15·39
$\Delta H_{\text{t}}^{\text{g}\rightarrow\text{H}_2\text{O}}(\text{H}^+)$[c]	−270·0	−270·0
$\Delta H_{\text{t}}^{\text{g}\rightarrow\text{DMSO}}(\text{BH}^+)$	−79·91	−71·47
$\Delta H_{\text{t}}^{\text{g}\rightarrow\text{DMSO}}(\text{B})$[b]	−17·28	−13·10
$\Delta H_{\text{t}}^{\text{g}\rightarrow\text{DMSO}}(\text{H}^+)$[c]	−276·1	−276·1

[a] Ref. 6.
[b] Table 1.
[c] Ref. 25.

Table 4 supports this assumption: $-71{\cdot}99$ kcal mol^{-4} more exothermic than $-66{\cdot}47$ kcal mol^{-1} (water) and $-79{\cdot}91$ kcal mol^{-1} more exothermic than $-71{\cdot}47$ kcal mol^{-1} (DMSO). The differences are also ordered correctly: $-71{\cdot}47 + 79{\cdot}91 = 8{\cdot}44$ kcal mol^{-1} and $-66{\cdot}47 + 71{\cdot}99 = 5{\cdot}52$ kcal mol^{-1}.

Hence all the available evidence points towards the explanation that the origin of the *N*-methylation effect in azoles is the loss of an active centre for solvation both in neutral molecules and in conjugated acids. The case with imidazoles can be represented in the following manner:



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