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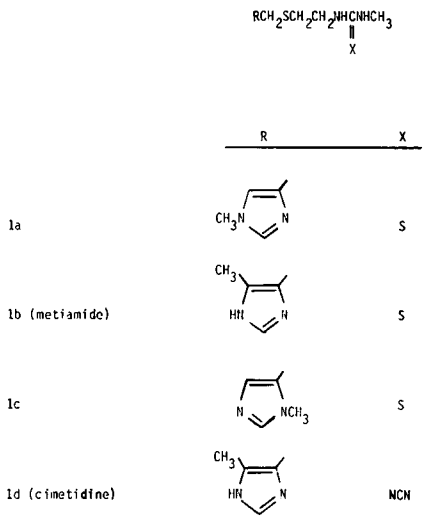
# COMMUNICATIONS

## The effect of intramolecular hydrogen bonding on the thermodynamics of partitioning of an isomer of the histamine $H_2$-receptor antagonist metiamide

R. C. MITCHELL*, D. DUNKLEY, *Smith Kline and French Research Ltd, The Frythe, Welwyn, Hertfordshire, UK*

The thermodynamics of transfer from water to 1-octanol of the 4 and 5 substituted *N*-methylimidazole isomers of the $H_2$-receptor antagonist metiamide have been determined. The isomers have similar free energies of transfer but the enthalpy and entropy of transfer of the 4-isomer are substantially greater than those of the 5-isomer. This indicates that the 4-isomer forms an intramolecular hydrogen bond in the polar octanol phase.

Infrared spectroscopic studies (Mitchell 1980) have shown that the 4-substituted *N*-methylimidazole isomer (1a) of the histamine $H_2$-receptor antagonist metiamide (1b), forms an intramolecular hydrogen bond in bromoform whereas the 5-substituted *N*-methylimidazole somer (1c) does not. Additionally, partition measurements (Mitchell 1980) have shown that in the chloroform–water solvent system the partition coefficient of 1a is almost four times greater than that of 1c, whereas n the 1-octanol-water solvent system the partition coefficient of 1a is slightly less than that of 1c. It was, therefore, tentatively concluded that 1a forms an intramolecular hydrogen bond in the chloroform phase but not in the polar 1-octanol phase. However, it has been shown recently that intramolecular hydrogen bonding can affect the $\Delta H$ and $\Delta S$ of the transfer process and have little affect on $\Delta G$ (Dearden & Bresnen 1982). Hence studies have now been carried out on the effect of temperature on the partition coefficients of 1a and 1c in the 1-octanol-water solvent system, in order to determine the above parameters.




### *Method*

A filter-probe method similar to that recently described by Tomlinson (1982) was used. Five identical variable temperature experiments were carried out on both 1a and 1c. The $pK_a$'s of 1a and 1c at 25 °C are 6·3 and 6·8 respectively (Graham, M. J., personal communication), so the aqueous phase was buffered at pH 9·2 (at 20 °C) in order to suppress ionization. There was no evidence of sample decomposition in any of the experiments. The partition results from two typical experiments are given in Table 1 and the mean thermodynamic parameters of transfer (derived from plots of log P against 1/T) are summarised in Table 2.

Table 1. The effect of temperature on the partition coefficients (P) of 1a and 1c in the 1-octanol-water[a] solvent system.

| Temperature (K) | P 1a | 1c |
|---|---|---|
| 308 | 1·722 | 2·442 |
| 303 | 1·702 | 2·497 |
| 298 | 1·674 | 2·543 |
| 293 | 1·638 | 2·599 |
| 288 | 1·618 | 2·648 |

[a] 0·005 M borax/0·0006 M boric acid, pH = 9·2 at 20 °C.

* Correspondence.

Table 2. The enthalpies (ΔH), entropies (ΔS) and free energies (ΔG) of transfer of 1a and 1c from water to 1-octanol[a].

| | ΔH (KJ mol$^{-1}$) | ΔS (J mol$^{-1}$ K$^{-1}$) | ΔG (KJ mol$^{-1}$)[b] |
|---|---|---|---|
| 1a | +2·66 (0·16) | +13·1 (0·5) | −1·42 (0·02) |
| 1c | −3·29 (0·30) | −3·4 (0·9) | −2·24 (0·10) |

[a] The values are the means from 5 experiments; the standard deviations are given in parentheses.
[b] At 37 °C.

The partition coefficient of 1a is slightly less than that of 1c over the whole temperature range (288–308 K). Interestingly, however, the ΔH and ΔS of transfer are substantially *greater* for 1a than 1c. This strongly suggests that 1a *does* form an intramolecular hydrogen bond in 1-octanol, because similar partition studies on 2 and 4 substituted phenols (Dearden & Bresnen 1982) have shown that the ΔH and ΔS of transfer are *less negative where intramolecular hydrogen bonding occurs*, presumably due to a reduction in the hydrogen bonding interactions between the solute and 1-octanol.

Evidently, the solvating properties of 1-octanol attenuate the effects of intramolecular hydrogen bonding on ΔG. Therefore, reliable conclusions regarding the intramolecular hydrogen bonding properties of a solute in the 1-octanol-water solvent systems can only be drawn from measurements of ΔH and ΔS.

Finally, these results suggest that compounds related to 1a, such as the histamine $H_2$-receptor antagonists metiamide (1b) and cimetidine (1d), probably adopt intramolecularly hydrogen bonded conformations in much more polar environments than previously considered.

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# The rapid estimation of strychnine in tincture of nux vomica BP by high-performance liquid chromatography

R. DENNIS, *Pharmacognosy Research Laboratory, Department of Pharmaceutical Chemistry, Sunderland Polytechnic, SR1 3SD, UK*

Strychnine is separated from other alkaloids in nux vomica tincture in less than 6 min on a 12·5 cm Hypersil column using a mobile phase of methanol, 2 M ammonium hydroxide, M ammonium nitrate (27 : 2 : 1), uv detection at 254 nm. Quantitative estimation may be obtained by comparing peak area or height against an external standard (0·150% w/v strychnine base in 45% ethanol). The results obtained were comparable to those obtained by the BP method which takes 5 h.

The estimation of strychnine in tincture of nux vomica by the British Pharmacopoeia (BP) method is a spectrophotometric determination after a 4 h liquid–liquid extraction. Absorption methods of this type are lacking in specificity when alkaloids of similar structure occur together, as they do in this example. The rapid quantitative estimation of strychnine in tincture of nux vomica by a modification of the high-performance liquid chromatography (hplc) system used by Jane (1975) is now reported. Other hplc separations involving strychnine alkaloids have been described (Wu & Siggia 1972; Murgia & Walton 1975; Verpoorte & Baarheim Svendsen 1975; Twitchett 1975).

*Materials and methods*

All chemicals and reagents were reagent grade (BDH) with the exception of methanol (Analar). Standard strychnine and brucine solutions were 0·15% w/v in 45% ethanol.

Samples of nux vomica tincture obtained from different sources were assayed for strychnine by the BP method and then by hplc.

The chromatographic column (125 × 4·6 mm) was packed by upward displacement (Bristow et al 1977) with 5 μm Hypersil (Shandon Southern, Runcorn). A variable wavelength uv photometer (Pye Unicam, Cambridge) operating at 254 nm was used as a detector and a Minigrator (Spectra-Physics, St Albans) was used to measure peak areas and retention times. Samples (10 μl) were introduced onto the column using a Rheodyne injection valve (model 7125) fitted with a 10 μl loop. The eluent, methanol–2 M ammonium hydroxide–M ammonium nitrate (27 : 2 : 1) degassed under vacuum at ambient temperature and used at a flow rate of 2·0 ml min$^{-1}$ was delivered from an Altex 110 pump (Altex Scientific Inc., Berkeley, California). The chart recorder was a Leeds and Northrup XL flat bed recorder. Each result (Table 1) is the mean of three replicate determinations. Calibration plots were similarly determined using standard solutions of strychnine and brucine. Concentrations were calculated using either peak areas or heights.