Rate constants and activation parameters for ring–chain tautomerism in 5-, 6- and 7-ring-1,3-dinitrogen heterocycles

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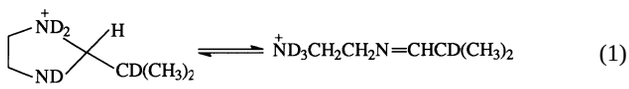
Free energies, enthalpies and entropies of activation have been measured for the ring–chain tautomeric equilibria existing in imidazolidine, hexahydro-pyrimidine and -diazepine ring systems under acid-catalysed conditions in a solvent consisting of 4:1 DMSO–D_2O using computer analysis of NMR signal bandshape.

Introduction

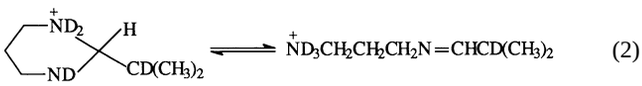
The aliphatic aldehydes, generated in biological tissues under oxidative stress,[1] are believed to cause pathophysiological damage to key proteins and enzymes by reacting with side chain functions, particularly the primary amine group of the lysine residues and the thiol group of cysteine residues.[2] As a step towards clarifying this complex situation we have recently investigated[3] the reaction between [2-^{2}H]2-methylpropanal and a series of α,ω-diamino-n-alkanes with a varying number of methylene groups in a solvent consisting of [$^2H_6$]dimethyl sulfoxide–^2H_2O (4:1). Using ^{1}H NMR spectroscopy, equilibrium constants for the formation of mono-imines, diimines and cyclic *gem*-diamines have been determined. In the course of this work we observed that the imidazolidine, hexahydropyrimidine and -diazepine ring systems were produced by cyclisation of the imines formed from the reactions of 1,2-diaminoethane, 1,3-diaminopropane and 1,4-diaminobutane, respectively, with 2-methylpropanal. It was noted that certain of their NMR resonances underwent a temperature dependent broadening, attributable to ring–chain tautomerism. For the imidazolidine and the hexahydropyrimidine systems the equilibrium lies towards the ring tautomer; for the hexahydrodiazepine it is the mono-imine chain structure which is the predominant form.

Very little quantitative work has been carried out on rates of reaction for such processes.[4] It is clear that acid catalysis is necessary since the ring closure is *endo-trig* according to the Baldwin rules,[5] unlike the similar cases in carbohydrate systems where ring closure is *exo-trig* and hence allowed. A study by Fife *et al.*[6] using the stopped-flow technique demonstrated that ring–chain tautomerism of an imidazolidine was the first step in its hydrolysis. Lambert *et al.*[7] confirmed this observation and determined the free energy of activation for the ring–chain equilibrium for 1,3-dimethylimidazolidine in trifluoroacetic acid solvent at 90 °C (70.7 ± 1.2 kJ mol^{-1}) using the NMR resonance coalescence technique. Attempts to measure this property for some other substrates (*e.g.* 1,3-dimethyl-2-phenylimidazolidine) were thwarted by the high temperatures required. A recent review[8] of quantitative measurements in ring–chain systems of 1,3-heterocycles concentrates on equilibrium constants for tetrahydro-1,3-oxazine (six-membered N,O) and oxazolidine (five-membered N,O) ring formation in solution, no precise measurements of rate constants appear to have been made in solution; indeed for 1,3-*N*,*N*-heterocycles very little quantitative data is available at all[3,4,9] and these are of equilibrium positions. The only recent report[10] of a rate measurement on a similar system gives an activation free energy for a ring–chain process in a tetrahydro-1,3-oxazine in the solid state.

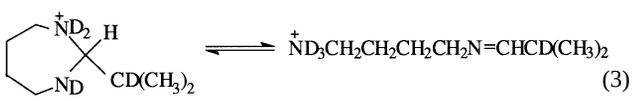
It was therefore of interest to examine, using NMR techniques, the rates of these ring–chain tautomeric processes in solution for the five-, six- and seven-membered 1,3-dinitrogen heterocycles where we have already obtained reasonably precise equilibrium constants [see equilibria (1)–(3)].



(1)



(2)



(3)

Experimental

All ^{1}H NMR spectra were obtained in 4:1 [$^2H_6$]DMSO–^2H_2O using excess 2-methylpropanal under acid (normally DCl) catalysed conditions in order to observe significant quantities of the species under investigation. 2-Methylpropanal was deuteriated at the 2-position to simplify the spectra. Full assignments of all NMR spectra are given in our earlier work,[3] together with a detailed discussion of all other equilibria present in these systems. Materials were the purest grade available (Aldrich) and distilled prior to use. [2-^{2}H]2-Methylpropanal was prepared from isobutenyl acetate[11] (details of its characterisation are given in ref. 3). The spectra were recorded on a Brucker AM 250 MHz spectrometer under controlled temperature conditions. Details of the precautions taken during preparation of solutions have been given previously.[3]

Results and discussion

2-Isopropyl-1,3-imidazolidine

The ^{1}H NMR spectrum (250 MHz) at 30 °C of a mixture of 0.06 mol dm^{-3} [2-^{2}H]2-methylpropanal and 0.01 mol dm^{-3} 1,2-diaminoethane, together with a little acid (~0.001 mol dm^{-3}), reveals broad signals at δ = 3.47 and 2.88. The former signal is

Table 1 First-order rate constants (k/s^{-1}) at different temperatures for the chain–ring (imidazolidine, hexahydropyrimidine) and ring–chain (hexahydrodiazepine) processes

2-Isopropyl-1,3-imidazolidine		2-Isopropylhexahydropyrimidine		2-Isopropylhexahydro-1,3-diazepine	
T/K	k/s^{-1}	T/K	k/s^{-1}	T/K	k/s^{-1}
273	3 ± 2	308	15 ± 3	263	3 ± 2
283	18 ± 3	313	20 ± 4	273	40 ± 10
293	58 ± 4	318	52 ± 5	283	120 ± 30
303	159 ± 5	323	115 ± 5	303	450 ± 100
313	490 ± 30	328	180 ± 10	313	2200 ± 200
323	1850 ± 3	333	410 ± 10	323	3.2 ± 1.0 × 10^4

Table 2 Free energies, enthalpies and entropies of activation for the equilibria

Compound	$\Delta G^{\ddagger}$/kJ mol^{-1} (298 K)	$\Delta H^{\ddagger}$/kJ mol^{-1}	$\Delta S^{\ddagger}$/J mol^{-1} K^{-1}
1,3-Imidazolidine	61.8 ± 0.1	88 ± 3.0	88 ± 10
Hexahydropyrimidine	70.8 ± 0.5	114 ± 7.0	145 ± 25
Hexahydro-1,3-diazepine	56.7 ± 1.0	91 ± 10	115 ± 40

attributed to the methine proton of the imidazolidine; the latter to its methylene protons in both the neutral and protonated form.[3] The signal broadening is due to the ring–chain tautomerism shown in equilibria (1).

On cooling to –10 °C the broad *gem*-diamine methine resonance sharpens to a normal width at $\delta = 3.42$ and no resonance is observed at δ ~7.8 (–N=C*H*–), showing within the limits of the NMR experiment that the equilibrium lies over to the left, *i.e.* favouring the ring tautomer. Because of overlap between the methine resonance and that of the methylene protons in another product (the corresponding diimine), an accurate computer simulation of the shape of the former would be difficult. However the signal at $\delta = 2.88$ due to the methylene protons in the cyclic species also sharpen to give an AA′BB′ quartet centred at $\delta = 2.90$. These peaks broadened and coalesced as the temperature was raised to 50 °C. This was attributed to the increase in the rate of mutual exchange between the two methylene groups of the ring compound through ring opening/closing. None of the other signals in the spectrum showed any dynamic effects as the temperature was raised, eliminating the possibility of other species being involved. Proton shifts arising from acid–base equilibria are much faster than the NMR timescale in these systems.

Computer simulation[12] of the shape of these methylene signals gave six rate constants at temperatures ranging from 273–323 K (Table 1); the corresponding Eyring activation parameters are given in Table 2.

2-Isopropylhexahydropyrimidine

To provide the best conditions for observing dynamic processes in this system, a solution consisting of 0.01 mol dm^{-3} [2-^{2}H]-2-methylpropanal, 0.01 mol dm^{-3} 1,3-diaminopropane and 0.003 mol dm^{-3} HCl was employed. The relevant equilibrium is shown in equilibria (2).

A slightly higher acid concentration was required in order to shift the signal for the methine proton of the hexahydropyrimidine away from that of the methylene groups attached to nitrogen in the diimine.[3] The signals arising from the C-4 and C-6 methylene groups in the 2-isopropylhexahydropyrimidine showed broadening and coalescence as the temperature was increased from 30–60 °C. The chemical shifts of these signals were 2.75 (triplet) and 3.06 (doublet, $J = 12.3$ Hz) which accords with our previous assignment.[3] The spectrum was taken at 5 °C intervals, giving finally a broad singlet at 60 °C. No other peaks showed any signs of exchange. Again the equilibrium effectively lies over to the ring structure under these conditions, since no mono-imine is observed. Computer simulation was carried out to give the rate constants (Table 1) and hence the Eyring activation parameters (Table 2) were obtained.

2-Isopropylhexahydro-1,3-diazepine

This system is the only one of the three where the mono-imine chain structure predominates. The relevant ^{1}H NMR assignments are set out in Scheme 3 of Ref. 3. At a temperature of −20 °C the signals due to the methylene groups adjacent to amino nitrogen occur at $\delta = 2.76$, those due to methylene adjacent to imino nitrogen at $\delta = 3.28$ and the –N=C*H*– signal (diimine) at $\delta = 7.54$. As the temperature increased the $\delta = 2.76$ and 3.28 signals decrease in size being replaced by a broad singlet centred at $\delta = 3.02$ (30 °C), sharpening further at 60 °C. Monitoring of the concentrations of the different species demonstrated that the decrease in intensities of the signals at $\delta = 3.28$ and 2.70 was compensated by the increase of the signal at $\delta = 3.02$. Clearly the two different mono-imine methylene peaks adjacent to nitrogen are exchanging at the higher temperature *via* the hexahydrodiazepine. The behaviour of the mono-imine –C*H*=N– signal at $\delta = 7.57$, which can be distinguished from the corresponding one in the diimine at $\delta = 7.54$, also behaves as expected. At –20 °C, this signal is sharp; as the temperature is increased it broadens, obscuring that of the diimine; finally it sharpens again at 60 °C with $\delta = 7.51$. This chemical shift should be a weighted average of the mono-imine singlet (7.57) and the methine in the unobserved hexahydrodiazepine ring, which is predicted to resonate at $\delta = 3.65$ (*cf.* 2-isopropylimidazolidine). Hence we can calculate the approximate population ratio for chain:ring. The computer fitting was carried out as before and the results are given in Tables 1 and 2. The lower precision in the energy, enthalpy and entropy terms arises from the unavoidable overlap of the $\delta = 7.54$ diimine signal.

The values of $\Delta G^{\ddagger}$ obtained are comparable to the values estimated (66–75 kJ mol^{-1}) by Lambert *et al.*[7] for some 2-substituted imidazolidines from coalescence temperature measurements at *ca.* 370 K. This latter work was carried out in trifluoroacetic acid as solvent so that all species are completely protonated. It is almost certain that in our experiments the equilibrium process for all three systems depends upon acid catalysis. Our previous measurements[3] of the dimensionless equilibrium constants for ring formation ($K_D = 2$ for the hexahydrodiazepine, 135 for the hexahydropyrimidine and 24 for the imidazolidine) show that the six-membered ring is significantly more stable than either the five- or seven-membered rings. It is reasonable therefore to ascribe the much higher free energy/enthalpy of activation for the six-membered ring opening to the lower ground state energy of this ring. The entropy measurements are of much lower accuracy and cannot be usefully compared: for instance the differences may well depend on differential solvation of the various species. Further investigation of the dependence of these rate processes on acidity will be interesting.

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