Volumes of Reaction for the Formation of Some Analogues of Tetrahedral Intermediates

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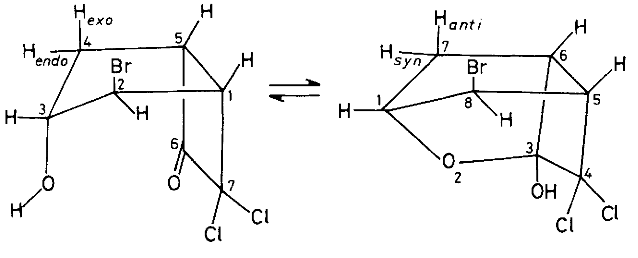
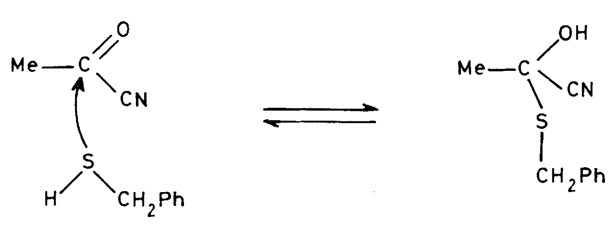
Two reactions which comprise equilibrium addition of a protic species to a carbonyl group, the hydroxyketone–hemiacetal interconversion (**1a**) $\rightleftharpoons$ (**1b**), and the thiol addition of acetyl cyanide (**2a**) $\rightleftharpoons$ (**2b**), have been studied by n.m.r. and their spectra thoroughly analysed. Equilibrium constants have been measured as a function of pressure to obtain volumes of reaction which relate to the formation of the 'tetrahedral intermediate' of ester hydrolysis. The intramolecular reaction is shown to have a much less negative volume change than the intermolecular analogue, pointing to the important contribution to ΔV and to $\Delta V^{\ddagger}$ of molecular association prior to bond formation.

The most commonly experienced mechanism for base-promoted ester hydrolysis ($B_{Ac}2$) takes place by co-ordination of a nucleophile to the carbonyl group and kinetic measurements refer to the activation parameters for that step.[1,2] In order to characterise the transition state more precisely, it would be desirable to measure the properties (*e.g.* change of energy, entropy, volume) for the overall addition reaction leading to the adduct ('tetrahedral intermediate'). These quantities are not normally accessible to measurement since the species are transient and are not even directly observable. There are, however, examples of analogous reactions in which the carbonyl adduct is a stable molecule in observable equilibrium with its precursors. Such cases would serve as models for the tetrahedral intermediates in ester hydrolysis. Two examples of this type of process are the hydroxyketone–hemiacetal equilibrium (**1a**) $\rightleftharpoons$ (**1b**)[3,4] and, a bimolecular example, the addition of nucleophiles such as thiols to acetyl cyanide (**2a**) $\rightleftharpoons$ (**2b**).[5] An additional advantage in studying these reactions is the comparison which may be made between volume changes for unimolecular and bimolecular processes which should enable an estimate to be made of the contributions from molecular association and actual bond formation. In each case, volume changes associated with the reactions can be estimated by measurement of the pressure dependence of the equilibrium constant. We report the first measurements of volume changes on this type of reaction, n.m.r. spectroscopy being used for the determination of the equilibrium constants. The rates of interchange between (**1a**) and (**1b**) are rapid so that n.m.r. measurements were made at a series of elevated pressures. The equilibrium of the bimolecular reaction is only slowly attained and, in this case, samples could be equilibrated under pressure and withdrawn for analysis by n.m.r.



(**1a**) (**1b**)



(**2a**) (**2b**)

Experimental

Acetyl cyanide was commercial material (Fluka) and used as supplied. 2-*exo*-Bromo-7,7-dichloro-3-*endo*-hydroxybicyclo[3.2.0]heptan-6-one (**1**) was prepared according to the method of Grudzinski and Roberts[3] from the adduct of dichloroketene to cyclopentadiene. A complete ^{1}H n.m.r. analysis was performed on this six-spin system in order to identify unambiguously the resonances of the two isomeric species present. Details of this analysis are given in Figures 1—4. The spectrum of the species (**1a**) and its tricyclic isomer (**1b**) were measured from the equilibrium mixture of the two. Table 1 sets out coupling constants for all protons.

^{1}H *N.m.r. Analysis of* (**1**).—The proton spectrum of (**1**) has been previously reported at 100 MHz,[3] the analysis being based partly on analogy with similar compounds. We undertook a more detailed study at 250 MHz in order to obtain independent proof of the proton assignments. The 250 MHz spectrum in deuteriochloroform ($CDCl_3$) reveals 11 complex multiplets and highly variable additional peaks due to the hydroxylic protons. A COSY two-dimensional spectrum enabled the 11 multiplets to be assigned to two separate six-spin systems (Figure 1). This information, together with a detailed analysis and simulation of the resolution-enhanced one-dimensional spectrum (Figure 2), enabled all the spectral parameters for each spin system to be obtained (Table 1). It is particularly noteworthy that all the fifteen possible couplings are observed for one six-spin system [assigned below to (**1b**)] and fourteen for (**1a**). The differences in coupling constants for corresponding proton–proton interactions in the two systems were consistent with changes in the

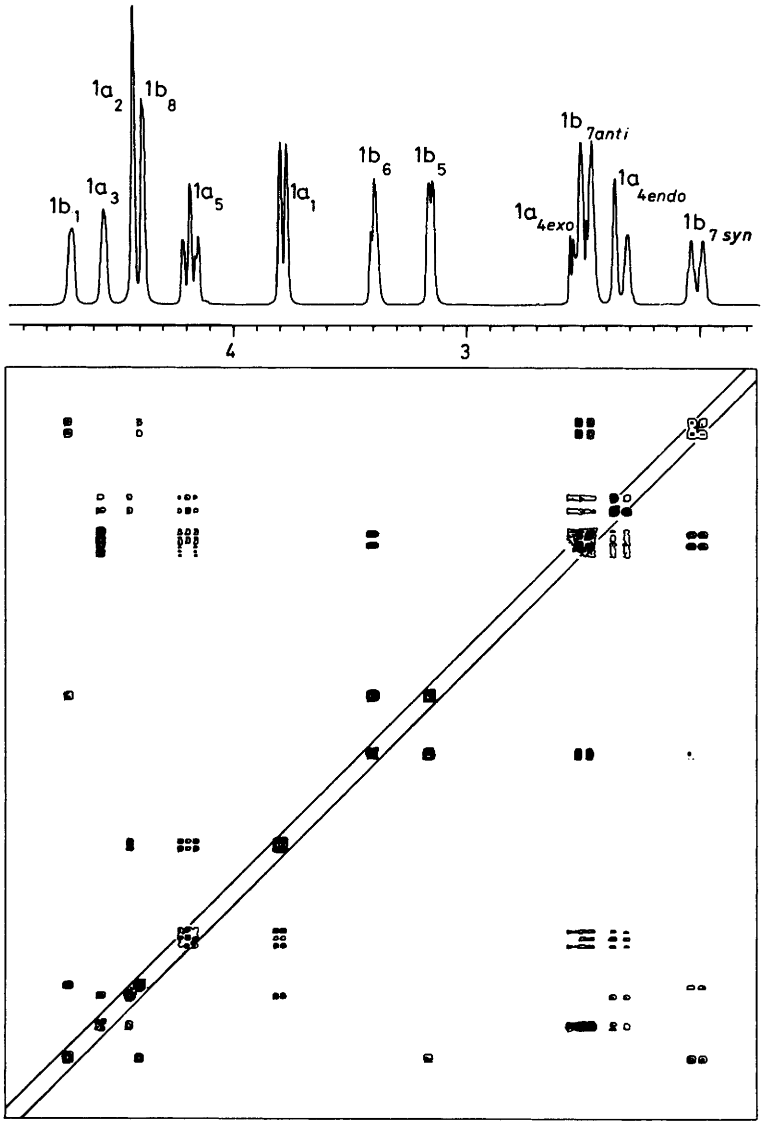


Figure 1. COSY spectrum of (**1a**) $\rightleftharpoons$ (**1b**) in $CDCl_3$ showing the presence of two six-spin systems. The data size was 512 × 512 points with a digital resolution of 1.56 Hz per point. Data were weighted by sine bell apodisation in both dimensions prior to Fourier transformation, and symmetrised before plotting

Table 1. ^1H N.m.r. parameters for (**1a**) and (**1b**) in pure $CDCl_3$ at room temperature

			(**1b**)					
			5	8	1	7_{syn}	7_{anti}	6
		δ/p.p.m.	3.194	4.419	4.732	2.058	2.530	3.466
(**1a**)	1	3.826		0.25	1.19	0.53	0.30	4.51
	2	4.466	0.90		1.78	1.14	0.21	0.10
	3	4.592	0.54	1.21		2.08	0.44	1.30
	4_{endo}	2.384	0.58	1.21	1.20		−12.16	1.49
	4_{exo}	2.544	0.33	0.33	3.62	−14.24		1.54
	5	4.223	7.60	0.25	0.0	1.10	8.40	

dihedral angles between (**1a**) and (**1b**) indicated by models and predicted by the Karplus relationship.[6] Although this provides a provisional assignment of the two spin systems, more direct proof of its correctness was obtained by measuring the spectrum in hexadeuteriodimethyl sulphoxide ([$^2H_6$]DMSO). In this solvent, exchange of the hydroxylic protons is sufficiently slow that their couplings with adjacent protons may be observed. A signal due to OH at δ 5.95 indeed shows the presence of two couplings, each of $J \sim 2$ Hz, and a difference decoupling experiment reveals these to be due to (**1a**) (3-H) and (**1a**) (*exo*-4-H), the latter being assigned to that of a 'w' conformation. The other hydroxylic resonance at δ 8.1 shows no coupling as would be expected from structure (**1b**) (Figure 3).

^{13}C *N.m.r. Analysis of* (**1**).—Riddell and his co-workers[7] have previously assigned the ^{13}C spectrum on the basis of ^1H off-resonance experiments but they were not able to distinguish between C-1, C-2, and C-5 in (**1a**) and between C-5, C-6, and C-8 in (**1b**). In order to clarify this assignment, we carried out a ^1H–^{13}C shift-correlated two-dimensional experiment which, together with the known ^1H assignments, enables a complete analysis of the ^{13}C spectrum to be made (Figure 4).

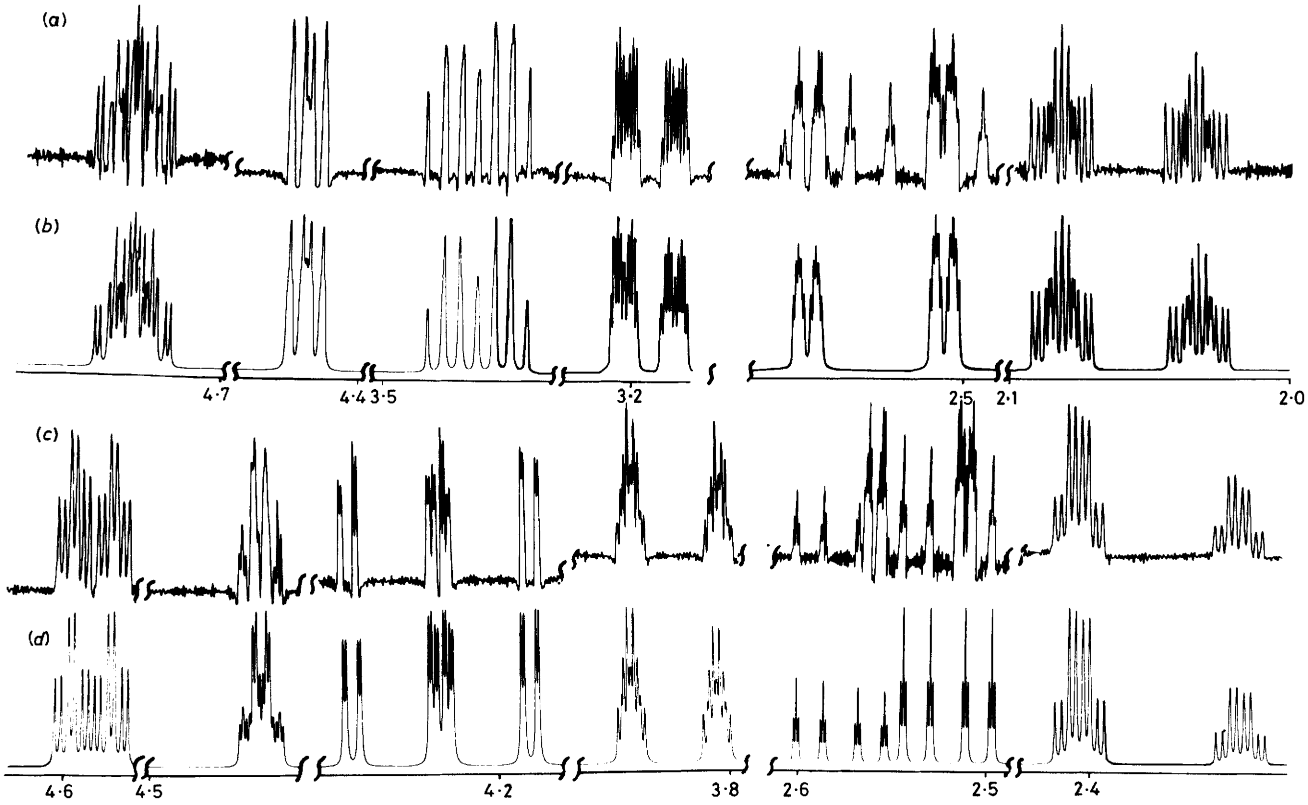


Figure 2. (*a*) Observed and (*b*) calculated spectrum for (**1a**). (*c*) Observed and (*d*) calculated spectrum for (**1b**). The free induction decay (F.I.D.) was recorded at a digital resolution of 0.05 Hz per point and was 'resolution enhanced' using a Gaussian weighting prior to Fourier transformation. The calculated spectra were obtained using a linewidth of 0.15 Hz

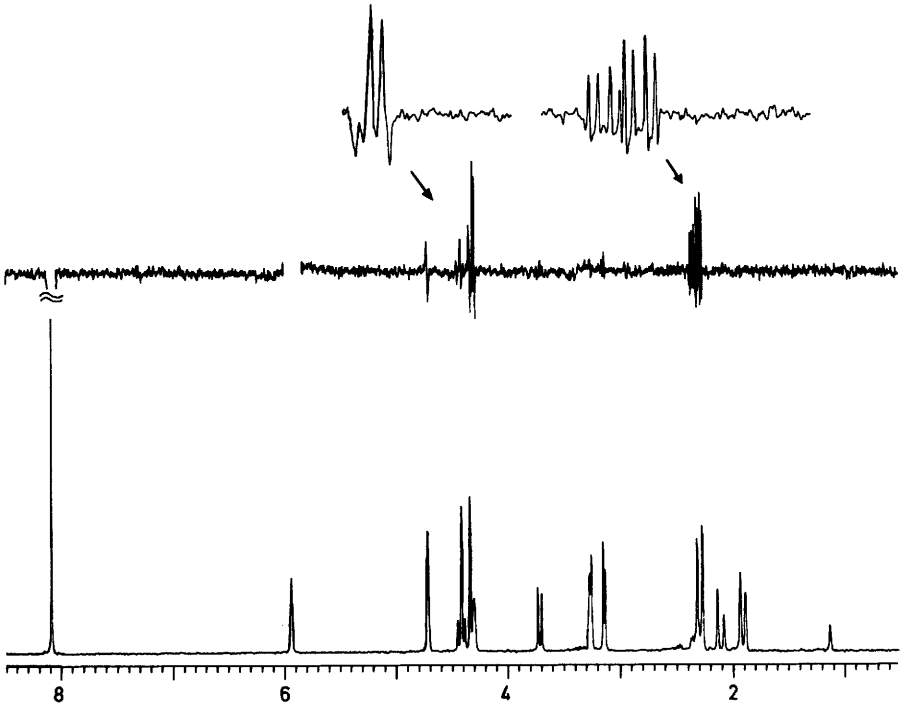


Figure 3. Double resonance difference spectrum of (**1a**) and (**1b**) in [$^2H_6$]DMSO. An F.I.D. recorded with a decoupler offset 10 Hz off-resonance from the OH peak at $\delta = 5.95$ was subtracted from one recorded with the decoupler on resonance. The multiplet due to (**1a**) *exo*-4-H is clearly revealed free of peaks due to (**1b**) 7-H

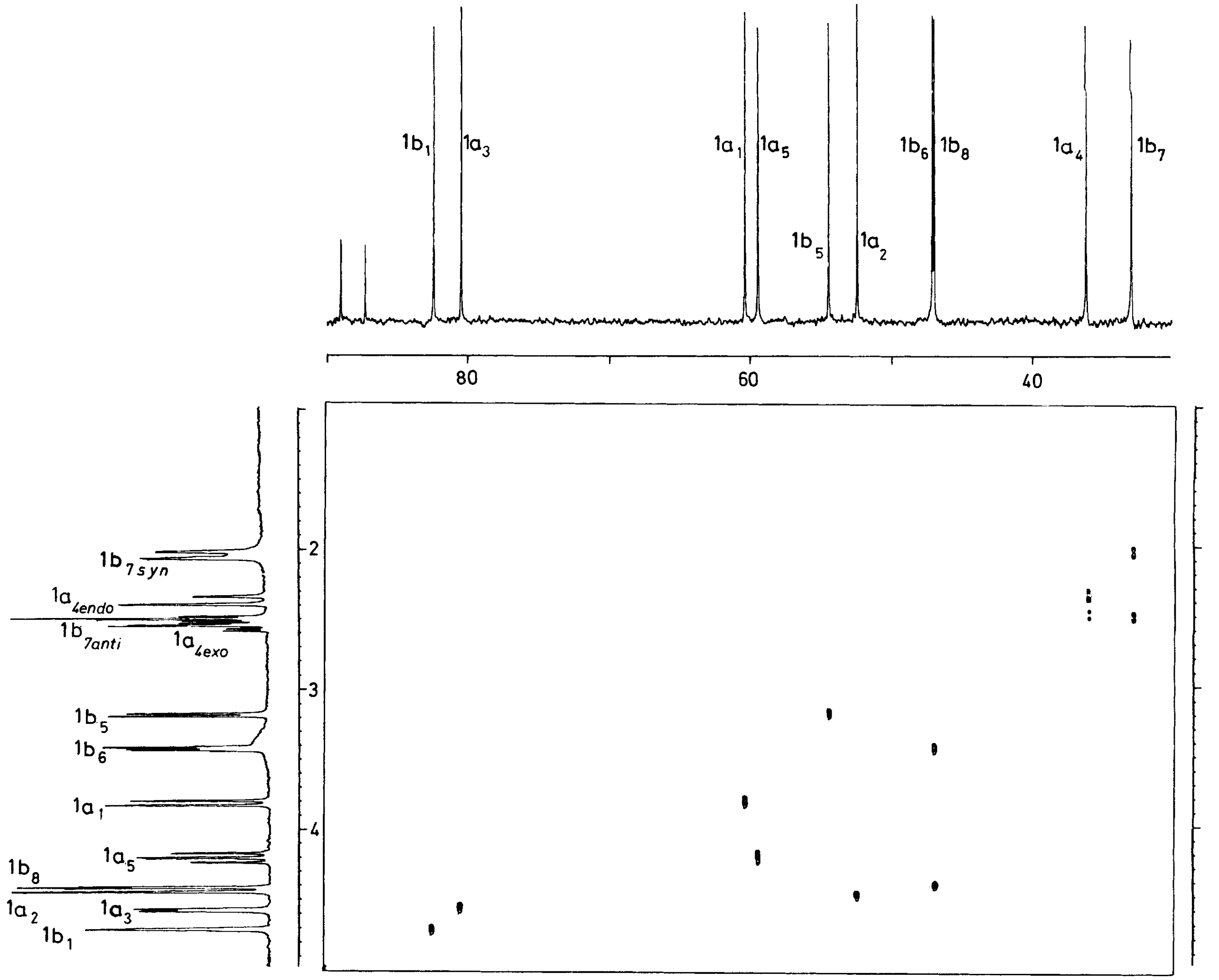


Figure 4. A $^1H-^{13}C$ shift-correlated spectrum of (**1a**) $\rightleftharpoons$ (**1b**) in $CDCl_3$. The final data matrix was 1k × 512 points weighted by shifted sine bell apodisation prior to Fourier transformation. The ^{13}C and ^1H chemical shift axes were 5 000 Hz and 800 Hz respectively

Temperature Dependence of the (**1a**) $\rightleftharpoons$ (**1b**) *Equilibrium.*—Riddell and his co-workers reported the ratio of [(**1a**)]/[(**1b**)] in pure $CDCl_3$ to be unity as a result of strong intermolecular hydrogen bonding between the two forms {giving a dimeric species, [(**1a**) • • (**1b**)]}. When a trace of acid was added the ratio was found to differ from unity. The ketone (**1a**) is the major species and its concentration increases with decreasing temperature. An analysis of the reported ratios in terms of equation (1) gives values of $\Delta H = -9.38 +/- 1.2$ kJ mol^{-1} and $\Delta S = -30.8 +/- 4.6$ J K^{-1} mol^{-1}.

$$\ln [(\mathbf{1a})]/[(\mathbf{1b})] = -\Delta H/RT + \Delta S/R \qquad (1)$$

Our studies in either pure DMSO or in 20% w/w DMSO–$CDCl_3$ also indicated non-integral ratios for [(**1a**)]/[(**1b**)] but with the hemiacetal (**1b**) the major species. Values are given in Table 2 and lead to values of $\Delta H = +11.47 +/- 0.96$ kJ mol^{-1} and $\Delta S = +32.3 +/- 5$ J K^{-1} mol^{-1}. This result is of similar magnitude but of opposite sign to that of the other workers. In our solvent system, in which hydrogen bonding is significantly disrupted, we find (**1a**) to have the greater entropy, consistent with the greater degree of freedom which this species might be expected to possess. It is possible that in the system studied by Riddell *et al.*, the acid catalyst actively promotes both inter- and intra-molecular hydrogen bonding between (**1a**) and (**1b**) resulting in different thermodynamic behaviour.

While these measurements were made at 250 MHz, the high-pressure n.m.r. system (Bruker CXP200) operated at 200 MHz with no spinning of the sample and consequently somewhat inferior homogeneity (giving *ca.* 2 Hz resolution). The resonances of corresponding protons in (**1a**) and (**1b**) which were most easily resolved and integrated were those of (**1a**) (*endo*-4-H):(**1b**) (*syn*-7-H) and (**1a**) 1-H:(**1b**) 5-H, and these were used for the measurements of equilibrium constants under pressure, the two measured ratios giving good agreement (Figure 1). Solutions of (**1**) were placed in the pressurisable probe of the n.m.r. spectrometer already described[8] and spectra recorded at several pressures between 1—2 000 bar. In each case, 20—30 scans were accumulated to obtain integral ratios reproducible to *ca.* 3% from which the populations of the two isomers and the equilibrium constants were obtained (Table 2).

An n.m.r. analysis of the equilibrium system acetyl cyanide–phenylmethanethiol has been published[5] and the equilibrium constant for formation of the adduct (**2b**) may conveniently be obtained from the ratio of the benzylic or methyl protons which for (**2a**) and (**2b**) differ sufficiently in their chemical shifts. In a typical experiment acetyl cyanide (16.8 mmol), phenylmethanethiol (8.46 mmol), and $CDCl_3$ (61.3 mmol) were mixed and a

Table 2. Equilibrium constants as a function of temperature and pressure

(i) (**1a**) $\rightleftharpoons$ (**1b**); solvent: 20% w/w DMSO–$CDCl_3$

T/K	K = [(**1b**)]/[(**1a**)]
305	1.85
295	2.22
285	2.74
275	3.23
265	3.57

(ii) (**1a**) $\rightleftharpoons$ (**1b**); T = 301.6 K; solvent: 20% w/w DMSO–$CDCl_3$

p/bar	K = [(**1b**)]/[(**1a**)]		K_{rel}
	syn-7-H/*endo*-4-H	5-H/1-H	
1	2.10	2.10	1.00
		2.15	
1 000	2.57	2.72	1.21
2 000	2.71	2.79	1.27
	2.86	2.78	

$\Delta V = -3.2 +/- 0.5\ cm^3\ mol^{-1}$
$K_0 = 2.19 +/- 0.07$

(iii) (**2a**) $\rightleftharpoons$ (**2b**); T = 303 K; solvent: $CDCl_3$

p/bar	K'/m^{-1}	K_{rel}
1	1.80	1.00
500	2.35	1.305
530	2.48	1.38
630	2.56	1.42
860	2.84	1.58
1 140	3.46	1.92

$\Delta V = -13.0 +/- 0.5\ cm^3\ mol^{-1}$

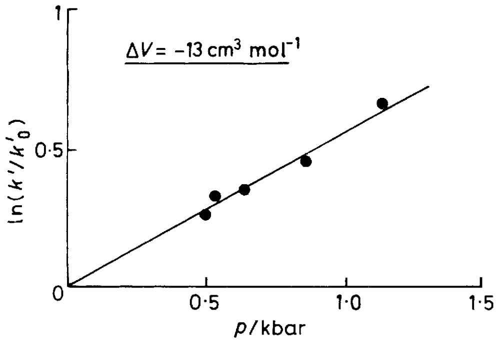


Figure 5. Plot of ln K'_{rel} against pressure for the equilibrium (**2a**) $\rightleftharpoons$ (**2b**)

sample (*ca.* 0.5 ml) placed in a cylindrical container of PTFE closed with a tightly fitting plunger of the same material. Air was swept out and the container was closed and sealed into a stainless steel cylinder which was immersed in a water thermostat at 30 +/− 0.2 °C and was pressurised by pumping in hydraulic oil, the pressure being measured by an accurate Bourdon gauge. The sample was allowed to remain under pressure for 48 h, sufficient for the establishment of equilibrium, after which it was removed and the ^1H n.m.r. spectrum at 220 MHz was recorded. A series of such experiments at pressures between 1—1 250 bar was carried out and the equilibrium constant for the reaction as a function of pressure determined (Table 2). As this is a bimolecular reaction equilibrium constants K' were expressed in molalities (m) which require no correction for compressibility, equation (2):

$$K' = m_{adduct}/m_{PhCH_2SH} \cdot m_{MeCOCN} \qquad (2)$$

The volumes of reaction were calculated from equation (3):

$$\Delta V = -RT\,d\ln K'/dp_{p \to 0} \qquad (3)$$

In neither case was curvature of a plot of ln K' against p discernible and therefore equation (3) was assumed to be linear (Figure 5).

Discussion

Volumes of reaction for the two examples are both negative as expected since the forward reactions are associative processes. However, the values are strikingly different even allowing for the difference of solvent. The intramolecular reaction shows a far less negative volume change than does the intermolecular equivalent. Solvation differences may account for a part of this discrepancy since in equilibrium 1 a hydroxy function is present in both reagent and product, while in 2 a thiol is exchanged for the more powerful hydrogen-bond donor, hydroxy. However, the volume change associated with hydrogen-bond formation is quite small (*e.g.* phenol–dioxane, $-3.2\ cm^3\ mol^{-1}$ [2]) so the difference in hydrogen-bonding capacity between SH and OH would seem inadequate to account for a difference of 10 $cm^3\ mol^{-1}$ in ΔV. Moreover $CDCl_3$ does not have strong hydrogen-bond-acceptor capabilities. The results tend to support a long-harboured suspicion that a volume contraction accompanies the association of independent molecules irrespective of whether or not bond formation occurs. An additional reduction in volume is further to be associated with actual covalent bond formation. The latter possibly accounts for all the volume of reaction of (**1**). Thus, very crudely, molecular association may be assumed to account for a volume change of $-10\ cm^3\ mol^{-1}$ and bond formation for $-3\ cm^3\ mol^{-1}$. This expression is related to the observation that partial molar volumes of a given structural element are greater in a cyclic system than in a linear one. For example, a methylene group occupies 16 $cm^3\ mol^{-1}$ in a linear structure but 19 $cm^3\ mol^{-1}$ in a cyclic one. The reason for this has been shown to reside in differences in 'expansion volumes' V_e that component of the molar volume which is derived from thermal motions and freedom of vibration.[9,10] A more extreme case of this phenomenon is the actual increase in volume of the enolic form of ethyl acetoacetate compared with the oxo tautomer (by 1—2 $cm^3\ mol^{-1}$) whereas intermolecular hydrogen-bond formation is normally found to be accompanied by a decrease of volume of 3—5 $cm^3\ mol^{-1}$.[11] In the present case the magnitudes of the volume changes are both more negative since the reaction involves covalent bond formation but a difference between the intra- and inter-molecular processes remains.

It would be desirable to compare these volumes of reaction with the known volumes of activation for ester hydrolysis by the $B_{Ac}2$ mechanism. Since this reaction is necessarily carried out in at least partly aqueous solution, a problem arises as to the solvent effect. The hydrolysis of ethyl acetate in aqueous acetone has been studied under pressure and with variable composition of the medium.[12] Values of $\Delta V^{\ddagger}$ are reported as -9, -13, and $-17\ cm^3\ mol^{-1}$ for 80, 70, and 57% water, respectively. The volume of reaction for the second equilibrium, $-13\ cm^3\ mol^{-1}$, is of similar magnitude and is consistent with a transition state for ester hydrolysis in which association and partial bonding between base and ester is occurring. By contrast, the intramolecular example (1) is clearly not a good model for this reaction but would be so for a reaction such as lactonisation.

Acknowledgements

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