Reprinted from the
AUSTRALIAN JOURNAL OF CHEMISTRY

THE EFFECT OF PRESSURE ON CYCLIC REACTIONS

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[*Manuscript received December* 21, 1966]

Summary

Rates of the cyclization of 4-chlorobutanol and of some analogous non-cyclic solvolysis reactions have been measured in water, methanol, and aqueous acetone at pressures up to 3000 atm. The volume of activation of the cyclic reaction is less negative than those of the linear reactions, in each solvent, but it is suggested that the transition states of both types of reaction may be solvated to about the same extent. The volume of activation for the formation of an eight-membered ring in the cyclization of 4-bromobutylcatechol monoether was also determined.

Introduction

The effect of pressure on reactions in which cyclic transition states are formed has recently been reviewed.[1,2]

The volume of activation ΔV^* of such reactions is sometimes less negative than would be expected for the formation of a cyclic transition state from linear molecules, and it has been suggested that some of the solvent is excluded from the centre of a small ring,[3,4] thus adding to the effective volume of the transition state.

In the present work we have examined the cyclization of 4-chlorobutanol to form tetrahydrofuran. This reaction can be described as an internal S_N2 reaction and, like bimolecular S_N2 reactions, it proceeds by a highly polar transition state which is formed from neutral reactants. Thus a strong solvent effect on the rate of reaction is expected. We measured the rate over a range of pressures and solvents and, to have a valid comparison with analogous non-cyclic reactions, we measured a number of solvolysis reactions over the same range. We also measured the pressure effect on the cyclization of 4-bromobutylcatechol monoether (BBCE) in which an eight-membered ring is formed.[5]

Most of the cyclic reactions for which ΔV^* has been determined involve either neutral molecules and largely non-polar transition states, or ions in which the charge is maintained in the transition state.[1,2] For either type of reaction the solvent effects are small compared with those in S_N2 reactions in which highly polar transition states are formed from neutral molecules. In the discussion we have used a model of

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[1] Whalley, E., *Adv. phys. org. Chem.*, 1964, **2**, 93.

[2] Hamann, S. D., *Ann. Rev. phys. Chem.*, 1964, **15**, 345.

[3] Whalley, E., *Trans. Faraday Soc.*, 1962, **58**, 2144.

[4] Le Noble, W. J., *J. Am. chem. Soc.*, 1960, **82**, 5253.

[5] Ziegler, K., Lüttringhaus, A., and Wohlgemuth, K., *Liebigs Ann.*, 1937, **528**, 162.

Aust. J. Chem., 1967, **20**, 1335–42

transition state solvation suggested by Gonikberg and El'yanov[6] to interpret the volumes of activation of the reactions.

EXPERIMENTAL

Solvents

Methanol was dried by reaction with magnesium formate followed by distillation from anhydrous copper sulphate and from benzoic acid.[7] It was stored under anhydrous conditions. Acetone was purified by refluxing with potassium permanganate, dried, and fractionated. Water was distilled, boiled, and then deionized by passage through a bed of Biodemineralite resin for immediate use.

Reagents

The alkyl halides were B.D.H. laboratory grade reagents and were dried by chemical means and then fractionally distilled. Benzyl chloride was also B.D.H. laboratory grade material; it was dried and fractionally distilled under reduced pressure. The 4-chlorobutanol was prepared from redistilled tetrahydrofuran[8] and was redistilled as required.

The 4-bromobutylcatechol monoether (BBCE) was prepared by the method described by Lüttringhaus[9] from catechol and 1,4-dibromobutane. The product appeared to contain some catechol (Found: Br, 31·8. Calc.: Br, 32·4%), but we found that the rate of the alkaline cyclization of BBCE was not affected by even an excess of catechol.

Pressure Equipment

Pressure was generated by hand-operated oil pumps and was measured on Bourdon gauges to an accuracy of about 1%. The pressure vessel was similar in design to those used by Buchanan and Hamann[10] and by Koskikallio and Whalley,[11] but used a Pyrotenax thermocouple lead sealed through the pressure plug both for temperature and conductance measurements within the pressure vessel. For some reactions samples were withdrawn through a stainless-steel capillary sealed through the pressure plug. This carried the syringe-like PTFE reaction vessel on the high-pressure side and was closed by a small high-pressure valve at the low-pressure end.

The pressure vessel was immersed in an oil-bath which was maintained within 0·03° of the required temperature. Kinetic measurements were not begun until a differential thermocouple showed that thermal equilibrium between the inside of the pressure vessel and the bath was established. This usually took between 30 and 45 min from the time of altering the pressure. Measurements at atmospheric pressure were also made in the pressure vessel.

Kinetic Measurements

All but one of the reactions were followed conductimetrically in all-glass conductance cells. These cells were made by sealing platinum electrodes through the sides of sealed-off 20-ml syringes; they had a cell constant of 0·4–0·6 cm^{-1} and functioned well up to 3000 atm.

The cyclization of BBCE was followed by withdrawing small samples under pressure and estimating the liberated bromide ions by potentiometric titration with silver nitrate.[12]

RESULTS

The results and the reaction conditions of our rate measurements are given in Table 1. In Table 2 we give the values of ΔV^* derived graphically from plots of $\log k$ against pressure.

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[6] Gonikberg, M. G., and El'yanov, B. S., *Izv. Akad. Nauk SSSR, Otd. khim. Nauk*, 1960, 629.

[7] Grunwald, E., Jumper, C. F., and Mieboom, S., *J. Am. chem. Soc.*, 1962, **84**, 4662.

[8] Blatt, J., *Org. Synth.*, 1943, Coll. Vol. II, 571.

[9] Lüttringhaus, A., *Liebigs Ann.*, 1937, **528**, 276.

[10] Buchanan, J., and Hamann, S. D., *Trans. Faraday Soc.*, 1953, **49**, 1425.

[11] Koskikallio, J., and Whalley, E., *Trans. Faraday Soc.*, 1959, **55**, 809.

[12] Shiner, V. L., and Smith, M. L., *Analyt. Chem.*, 1956, **28**, 1043.

The cyclization of 4-chlorobutanol in water was found by Heine *et al.*[13] to have a rate constant of $2\cdot87\times10^{-4}$ sec^{-1} at $70\cdot5°$. More recent measurements[14] at $50\cdot3°$ have shown a rate constant of $3\cdot60\times10^{-5}$ sec^{-1} in good agreement with our measurements at atmospheric pressure. Our values of ΔH^* and ΔS^* are in agreement with the earlier measurements.[13] The values of ΔV^* in Table 2 show that the acceleration by pressure is comparatively small and decreases with increasing pressure. The acceleration is greater in 50% by volume acetone/water and is much greater again in methanol.

The neutral hydrolyses of methyl bromide, ethyl bromide, and n-butylchloride in water are closely analogous to the cyclization reaction of CBL. The absolute rate constant for the reaction of methyl bromide was not determined because the initial concentration of methyl bromide was not known accurately. The relative values given in Table 1 should however be accurate as they were found by using the same solution at different pressures. Our rate constant for the hydrolysis of ethyl bromide is in good agreement with the results of Robertson *et al.*[15] The value of ΔV^* for the methyl bromide and ethyl bromide hydrolyses are very similar to the value of -14 ml/mole which can be derived from the measurements of these reactions by Strauss[16] in 80% by volume ethanol/water.

The rate constant found for the hydrolysis of benzyl chloride in 50% by volume acetone/water at 1 atm agrees with the value of $2\cdot2\times10^{-7}$ sec^{-1} extrapolated from the measurements of Bensley and Kohnstam[17] at higher temperatures. This reaction has recently been studied at several pressures in aqueous ethanol[18] containing up to $0\cdot4$ mole fraction ethanol. The volume of activation was found to vary between -17 and -23 ml/mole with change of solvent composition with a maximum at $0\cdot3$ mole fraction. The solvent used in our measurements contained $0\cdot20$ mole fraction of organic component (acetone) and ΔV^* was found to be the same as that found in aqueous ethanol of the same composition.[18] Although the reaction is classed as an S_N2 reaction,[19] it has some characteristics in common with S_N1 reactions and an unusually polar transition state has been postulated for it.[17] This is supported by the volume of activation which is comparable with that of the S_N1 hydrolysis of t-butyl chloride in the same solvent.

The rate constants for the hydrolysis of t-butyl chloride in 50% and in 92% by volume acetone/water ($0\cdot20$ and $0\cdot74$ mole fraction respectively) at atmospheric pressure agree with the values found by Winstein and Fainberg[20] at the lower concentration of acetone, and, by making a slight extrapolation, with those of Tommila *et al.*[21] at the higher concentration of acetone. The effect of pressure on this reaction

[13] Heine, R. W., Miller, A. D., Barton, W. H., and Greiner, R. W., *J. Am. chem. Soc.*, 1953, **75**, 4778.

[14] Swain, C. G., Kuhn, D. A., and Schowen, R. L., *J. Am. chem. Soc.*, 1965, **87**, 1553.

[15] Robertson, R. E., Heppolette, J., and Scott, R., *Can. J. Chem.*, 1959, **37**, 803.

[16] Strauss, W., *Aust. J. Chem.*, 1957, **10**, 381.

[17] Bensley, B., and Kohnstam, G., *J. chem. Soc.*, 1957, 4747.

[18] Hyne, J. B., Golinkin, H. S., and Laidlaw, W. G., *J. Am. chem. Soc.*, 1966, **88**, 2104.

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[20] Winstein, S., Fainberg, A. H., and Grunwald, E., *J. Am. chem. Soc.*, 1957, **79**, 5937.

[21] Tommila, E., Tilikainen, M., and Viopo, A., *Ann. Acad. Sci. fenn.* AII, 1955, No. 65, 1.

TABLE 1

KINETIC MEASUREMENTS AT HIGH PRESSURES

Pressures at which the experiments were conducted are in atmospheres and are printed in **bold** numerals

Temp.	Constant	Results at Stated Pressures					
(1) Cyclization of 4-Chlorobutanol in Water; $[\mathrm{CB}]_0$ 0·01M							
	P (atm)	**1**	**500**	**1500**	**3000**		
39·8°	10^5k_1 (sec^{-1})	1·03	1·15	1·35	1·67		
49·7		3·26	3·54	4·54	5·62		
54·7		5·48	6·15	7·78	9·80		
59·6		9·95	10·7	12·8	16·7		
50	ΔH_p^* (kcal mole^{-1})	22·1	22·3	22·9	23·4		
50	ΔS_p^* (e.u.)	−13·8	−12	−9	−7		
(2) Hydrolysis of n-Butyl Chloride in Water; $[\mathrm{Bu^nCl}]_0$ 0·1M							
		1	**1000**	**2000**	**3000**		
25·0	10^8k_1 (sec^{-1})	1·5			2·8		
40·1		7·8					
45·0		12·9			25·2		
65·0		96·5	137	167	186		
(3) Hydrolysis of Methyl Bromide in Water; $[\mathrm{MeBr}]_0$ 0·001M							
		1	**700**	**1500**	**3000**		
30·0	$k_{1,P}/k_1$ (±1%)	1·00	1·51	1·96	3·03		
(4) Hydrolysis of Ethyl Bromide in Water; $[\mathrm{EtBr}]_0$ 0·05M							
		1	**1000**	**1700**	**2000**	**3000**	
30·0	10^6k_1 (sec^{-1})	5·85	8·53	10·2	11·1	13·6	
(5) Cyclization of Chlorobutanol in Acetone/Water (50% v/v); $[\mathrm{CB}]_0$ 0·05M							
		1	**500**	**1000**	**1500**	**2000**	**3000**
25·09	10^7k_1 (sec^{-1})	3·95	4·63	5·60	6·55	7·43	9·03
(6) Neutral Hydrolysis of Benzyl Chloride in Acetone/Water (50% v/v); $[\mathrm{PhCH_2Cl}]_0$ 0·05M							
		1	**1000**	**1500**	**2500**		
25·1	10^7k_1 (sec^{-1})	2·38	4·90	6·60	10·3		
(7) Neutral Hydrolysis of t-Butyl Chloride in Acetone/Water (50% v/v); $[\mathrm{Bu^tCl}]_0$ 0·05M							
		1	**470**	**1020**	**1330**		
25·0	10^7k_1 (sec^{-1})	2·37	3·20	4·36	5·1		
(8) Neutral Hydrolysis of t-Butyl Chloride in Acetone/Water (90% w/w); $[\mathrm{Bu^tCl}]_0$ 0·1M							
		1	**1000**	**1500**	**2000**		
50·0	10^7k_1 (sec^{-1})	5·90	12·6	15·9	18·9		
(9) Cyclization of 4-Chlorobutanol in Methanol; $[\mathrm{CB}]_0$ 0·1M							
		1	**1500**	**3000**			
25·0	10^8k_1 (sec^{-1})	1·92	4·92	7·75			
40·0		17·1	41·1	69·7			
49·7		70					
59·6		238					
(10) Neutral Methanolysis of Ethyl Chloride in Methanol; $[\mathrm{EtCl}]_0$ 0·5M							
		1	**850**				
60·0	10^8k_1 (sec^{-1})	2·56	6·11				
(11) Neutral Methanolysis of t-Butyl Chloride in Methanol; $[\mathrm{Bu^tCl}]_0$ 0·05M							
		1	**500**	**1500**	**3000**		
25·0	10^7k_1 (sec^{-1})	7·3	12·6	22·7	49·5		
50·0		210	370	805			
(12) Cyclization of Bromobutylcatechol Monoether in Alkaline Methanol; $[\mathrm{BBCE}]_0$ 0·01M, $[\mathrm{OCH_3^-}]_0$ 0·05M							
		1	**450**	**750**	**1500**		
32·1	10^5k_1 (sec^{-1})	1·16	1·1	1·2	1·22		

has previously been measured by Buchanan and Hamann[10] and by Hyne *et al.*[18] in 80% by volume (0·43 mole fraction) aqueous ethanol and a value of $\Delta V^* = -22$ ml/mole can be derived from both sets of results. The large value of $-\Delta V^*$ found in 0·74 mole fraction acetone and its pronounced decrease with increase in pressure suggest that acetone takes part in the solvation of the transition state in this solvent.

The methanolysis of t-butyl chloride in methanol has been measured at atmospheric pressure by Winstein *et al.*[20] and our results agree with theirs. David and Hamann[22] measured the rate at 36° at pressures up to 15,000 atm, but their lowest pressure measurement was at 5000 atm and does not allow calculation of ΔV^* at low pressures. Their results are not inconsistent with our low pressure results and show that even at the highest pressures ΔV^* is still negative for this $S_{\mathrm{N}}1$ reaction. David, Hamann, and Lake[23] also measured the rate of the methanolysis of ethyl chloride in methanol at pressures up to 30,000 atm at 65°, and our measurements at 850 atm fit in with their lowest pressure value at 3000 atm and permit the calculation of a low pressure value of ΔV^*.

TABLE 2

VOLUMES OF ACTIVATIONS OF REACTIONS LISTED IN TABLE 1

Reaction	Temp.	ΔV^* (ml/mole)					
		1 atm	500 atm	1000 atm	1500 atm	2000 atm	3000 atm
(1)†	39·8°	−5·8	−5·2		−4·0		−3·7
	49·7	−7·2	−6·1		−4·3		−3·7
	54·7	−7·8	−6·8		−5·3		−4·0
(2)	65·0	−12		−7		−4	−2
(3)	30·0	−14·5		−10·0		−7·5	−6·5
(4)	30·0	−11·5		−7·5		−5·5	−4·5
(5)	25·1	−10·5		−8·0		−5·5	−4·0
(6)	25·1	−20		−15		−11	
(7)	25·0	−16·5	−14·8	−11·8			
(8)	50·0	−24		−15		−8	
(9)	25·0	−20		−14		−9	−6
	40·0	−20		−14		−10	−7
(10)	60·0	−32			−18		−6
(11)	25·0	−31		−20		−13	−10
	50·0	−33		−21			
(12)	32·1						

† See numbered headings in Table 1 for description of reactions.

The alkaline cyclization of 4-bromobutylcatechol monoether (BBCE) in methanol proceeds by a different mechanism to the other reactions[1] discussed in this paper.

The rate-determining nucleophilic attack by the negatively charged oxygen on the bromine carrying carbon is preceded by the equilibrium ionization of the

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[22] David, H. G., and Hamann, S. D., *Trans. Faraday Soc.*, 1954, **50**, 1188.

[23] David, H. G., Hamann, S. D., and Lake, S. J., *Aust. J. Chem.*, 1955, **8**, 285.

phenolic hydrogen. Both the initial and the transition state therefore carry a charge, and the reaction has its bimolecular analogue in the reaction of n-butyl bromide with phenoxide ion which was investigated by Brower[24] in ethanol. Brower's results give a value of $\Delta V^* = 11$ ml/mole for the linear reaction, while we find $\Delta V^* = 0$ ml/mole for the monomolecular cyclization after allowing for the change of ionization equilibrium with pressure.† Such a difference in ΔV^* has been found for the acid-catalysed lactonization of hydroxybutyric acid ($\Delta V^* = -2 \cdot 7$ ml/mole in water) compared with the acid-catalysed reaction of simple alcohols with acetic acid ($\Delta V^* = -9$ ml/mole).[3] For these reactions this difference has been attributed to the exclusion of solvent from the centre of the cyclic transition state,[3] and this may also be the case for the cyclization of BBCE. However, this effect would be expected to be smaller rather than greater for the eight-membered ring formed by BBCE than for the five-membered lactone.

Discussion

Gonikberg and El'yanov[6] have suggested a method of estimating an upper limit to the number of solvent molecules involved in the solvation of a highly polar transition state from the change of ΔV^* with pressure. It is assumed that the solvating molecules are incompressible compared to the bulk solvent, and that the intrinsic volume change[25] ΔV_1^* is constant in the pressure range considered. The pressure equivalent to the electrostriction around an ion has been estimated[26] to be of the order of 10,000 atm. Although electronic charges may not be fully developed, the electrostriction around the transition state will be similar[27] and the above assumption should hold for pressures up to about 3000 atm. One can then express the solvation part of the volume of activation,[25] ΔV_2^* as

$$\Delta V_2^* = -n(V_{\mathrm{s},P} - V_{\mathrm{s},10000}) \tag{1}$$

where $V_{\mathrm{s},P}$ is the molar volume of the solvent at pressure P,
$V_{\mathrm{s},10000}$ is the molar volume of the solvent at $(P+10^4)$ atm, and
n is the number of solvent molecules transferred to the solvation shell as the transition state is formed.

According to this equation, a plot of ΔV^* at various pressures against the molar volume of the solvent at the same pressures should be a straight line with slope $-n$. Our results in water and methanol give such straight lines within the error of ± 1 ml/mole of the value of ΔV^*. Gonikberg and El'yanov have shown the same for a number of Menschutkin reactions in a range of solvents.[6,28] In pure solvents the volume difference on the right-hand side of equation (*1*) can be calculated from

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† Assuming the concentration of base to be constant, it can be shown that the true rate constant k is related to the observed first-order rate constant k' by $k = k'(1 + 1/K[\text{base}])$. The value of K at different pressures was found by measuring k' at different concentrations of base.

[24] Brower, K. R., *J. Am. chem. Soc.*, 1963, **85**, 1401.

[25] Hamann, S. D., "Chemical Kinetics" in "High Pressure Physics and Chemistry". (Ed. Bradley.) Vol. II. (Academic Press: London 1963.)

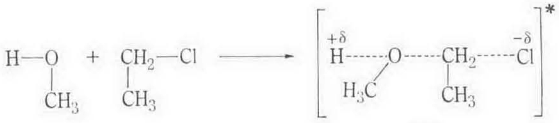
[26] Hepler, L. G., *J. phys. Chem.*, 1965, **69**, 965.

[27] Whalley, E., *J. chem. Phys.*, 1963, **38**, 1500.

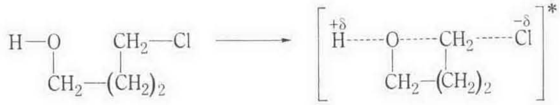
[28] Gonikberg, M. G., and El'yanov, B. S., *Dokl. Akad. Nauk SSSR*, 1960, **130**, 545.

compressibility data and with $P=1$, is found to be 3·6 ml/mole in water, 10 ml/mole in methanol, and 18 ml/mole in acetone at 25°.

It should be possible to find any special solvation effects connected with the formation of a cyclic transition state by comparing the cyclization reaction with analogous bimolecular reactions for which the intrinsic volume change[25] ΔV_1^* can be assumed to be the same. Thus in the transition states (I) and (II) the same bonds are broken and formed and hence ΔV_1^* will be the same for both.



(I)



(II)

There are at least three alternative ways of interpreting the observed difference in ΔV^*.

Although the transition states (I) and (II) are very similar, access of solvent to (I) may be easier than to the more rigid structure (II), and (I) may in fact be more strongly solvated.

The exclusion of solvent from the centre of the cyclic transition state could also account for the difference in volume and has been discussed in some detail by Le Noble[4] and Whalley.[1,3]

A further explanation is suggested by an argument analogous to one used by Kohnstam[19] in discussing the difference in entropy of activation of bimolecular and monomolecular solvolysis reactions. A difference between (I) and (II) is that a solvent molecule has been incorporated in (I) but not in (II). This molecule will have lost the "free volume", which is associated with any molecule in the liquid state, when it became attached to the transition complex. This loss of volume will be in addition to that due to the partial formation of a bond included in ΔV_1^*, and must be about the same as that due to the orientation and "freezing" of a solvating molecule; both are associated with similar loss of translational and vibrational degrees of freedom. In the case of the OH group of 4-chlorobutanol these degrees of freedom are already severely restricted in the initial state and their elimination in the transition state will cause only a small contraction in volume. The total volume change for the formation of (I) should thus be more negative than that for the formation of (II), and the difference should be about the same as the contraction which occurs when one solvent molecule enters the solvent shell.

In Table 2, reaction (1) can be compared with (2), (3), and (4), and reaction (9) with (10) and (11). The difference between ΔV^* for the cyclization of 4-chlorobutanol and ΔV^* for equivalent bimolecular solvolysis reactions is then found to be 4–6 ml/mole in water and 11–12 ml/mole in methanol. By equation (*1*) these differences correspond to the volume lost on transfer to the solvation shell of 1 molecule of methanol or 1·5 molecules of water.

Our present results do not enable us to decide between the alternative interpretations. It would seem that detailed partial molar volume measurements on model compounds would be required to do this.

If one compares the cyclization reaction in water and in methanol by means of equation (*1*) one finds, from the change of ΔV^* with pressure, that in both solvents $n = 2\text{–}2\cdot5$. In spite of the large differences in ΔV^* in the two solvents, the same number of solvent molecules seem to be involved.

The small variation in ΔV^* for the hydrolysis reactions with solvent composition in aqueous ethanol and aqueous acetone is in marked contrast with the large change of ΔS^* which occurs. Thus for the hydrolysis of ethyl bromide in water[15] $\Delta S^* = -5$ e.u., while in aqueous ethanol[29] $\Delta S^* = -25$ e.u. This large difference reflects the entropy gain in water due to disruption of solvent–solvent interactions by the polar transition state; in aqueous ethanol these interactions are already disrupted and the full entropy loss due to solvation is observed. Volume effects associated with these solvent–solvent interactions are thus not nearly as pronounced as the entropy effects. This is also shown by the partial molar volume of water, which changes little when ethanol or acetone are added to it up to a molar fraction of about 0·8. The compression measurements of Stutchbury[30] show that this still holds at 1000 atm.

ACKNOWLDEGMENTS

The authors thank Dr S. D. Hamann for some helpful criticism of the manuscript. D.J.O. wishes to thank the Colonial Sugar Refining Co. Ltd for financial assistance, and the University of Sydney for a University Research Scholarship. We also wish to thank Mr E. S. Merritt for his assistance in maintaining the high-pressure equipment.

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[29] Robertson, R. E., *Can. J. Chem.*, 1964, **42**, 1707.

[30] Stutchbury, J. E., *Aust. J. Chem.*, 1956, **9**, 536.