The Effect of Pressure on Rate and Equilibrium in Nucleophilic Addition to Mesityl Oxide

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Abstract: The rates of addition of water, methanol, ammonia, and thiophenol to mesityl oxide have been determined at various pressures up to 1360 atm, and the activation volumes derived therefrom. It is inferred that the transition state for acid-catalyzed hydration involves two water molecules. The addition–elimination equilibrium involving methanol has been approached from both sides, and the difference between forward and reverse activation volumes agrees with the measured volume of reaction. The acid-catalyzed addition of methanol appears to be mechanistically similar to that of water. The activation volume for addition of ammonia decreased by 8 ml/mole on change of solvent from water to methanol, and a zwitterionic transition state is postulated. The activation volume for thiophenoxide ion is surprisingly large and nearly independent of solvent composition. It is inferred that the carbon–sulfur bond is nearly complete in the transition state.

Although the mechanistic details of reactions involving addition to carbon–carbon double bonds have been intensively studied for several decades, there still are important questions unanswered, and recently some conclusions which once seemed firmly based have been thrown into doubt. It was long thought that the rate-determining step of acid-catalyzed hydration of simple olefins did not involve participation by water because the rate is approximately proportional to Hammett's acidity function, h_0; but Baliga and Whalley[1] have shown that the activation volume is substantially negative, and the opposite conclusion now seems inescapable. The Zucker–Hammett hypothesis has been challenged on more general grounds by Bunnett[2] who proposes another method for demonstrating the kinetic participation of water in aqueous reactions.

In contrast to the behavior of simple olefins it has been reported that α,β-unsaturated carbonyl compounds[3] have rates proportional to (H_3O^+) rather than h_0. It appeared to us that this case too might profitably be studied by determination of activation volumes, and to this end we have selected mesityl oxide as substrate. This well-behaved substance gives clean acid-catalyzed addition of water and alcohols as well as uncatalyzed addition of neutral or negatively charged nucleophiles. Furthermore, the position of equilibrium in the alcohol reaction permits rate measurement from either side. The possibility of using a single substrate for such a variety of reactions ought to justify a rather stringent interpretation of variations in activation volume.

The use of activation volumes in the study of reaction mechanisms has been amply reviewed,[4] and we will only briefly state the empirically validated principles. Reactions which on other grounds are thought to have a bimolecular rate-determining step involving no net change in the number of ionic charges are characterized by activation volumes in the range -5 to -15 ml/mole.[5] Contrariwise, the simple bond-breaking processes have positive activation volumes of comparable magnitude.[6] If the rate-determining step (or any preceding step back to the "starting material" as defined by the rate law) involves ionization or neutralization of charges, the change in the electrostriction of solvent contributes a component of 25–45 ml per ion pair. The smaller value is for water, and the larger for organic solvents of low polarity. There is some evidence that ionization or deionization in the transition state can be detected by testing the dependence of activation volume on solvent polarity.[7]

Results and Discussion

Acid-Catalyzed Addition of Water. The kinetic data for this reaction are listed in Table I. By dilatometry it was found that the over-all change in volume of the reaction system is -9 ml/mole, and the difference in molar volume of product and reactants in pure liquid form is also -9 ml. Both mesityl oxide and diacetone alcohol have considerable volumes of mixing with water (-7.5 ml/mole each) due to their influence on the structure of water,[8] but this effect could not be expected to vary during the activation process. We have taken the precaution of proving that it shows no over-all change. The volume of activation was determined to be -14.5 ml/mole. Since this figure considerably exceeds the final volume of hydration, we believe that the transitional substrate has partial bonds to a water molecule and a hydronium ion, and that proton transfer is concerted with the formation of the new carbon–oxygen bond. The results are strikingly similar to those obtained with the hydrolysis of two square-planar Pt(II) complexes[9] which had already been thought to coordinate with two water molecules in or prior to the rate-determining step.

Bell, Preston, and Whitney[3] investigated the kinetics of mesityl oxide hydration with various acid catalysts up to concentrations of 3 *M* and their data have been

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[1] B. T. Baliga and E. Whalley, *Can. J. Chem.*, **42**, 1019 (1964).

[2] J. F. Bunnett, *J. Am. Chem. Soc.*, **83**, 4956 (1961).

[3] R. P. Bell, J. Preston, and R. B. Whitney, *J. Chem. Soc.*, 1166 (1962).

[4] (a) S. D. Hamann, "High Pressure Physics and Chemistry," Vol. II, Academic Press Inc., New York, N. Y., 1963, pp 163–205; (b) S. D. Hamann, "Physico-Chemical Effects of Pressure," Butterworth and Co. (Publishers), Ltd., London, 1957; (c) S. D. Hamann, *Ann. Rev. Phys. Chem.*, **15**, 349 (1964); (d) E. Whalley, *Advan. Phys. Org. Chem.*, **2**, 93 (1964).

[5] J. Koskikallio and E. Whalley, *Can. J. Chem.*, **37**, 783 (1959).

[6] K. R. Brower, Bruce Gay, and T. L. Konkol, *J. Am. Chem. Soc.*, **88**, 1681 (1966).

[7] K. R. Brower, *ibid.*, **85**, 1401 (1963).

[8] G. Némethy and H. A. Scheraga, *J. Chem. Phys.*, **36**, 3401 (1962).

[9] H. E. Brower, L. Hathaway, and K. R. Brower, *Inorg. Chem.*, **5**, 1899 (1966).

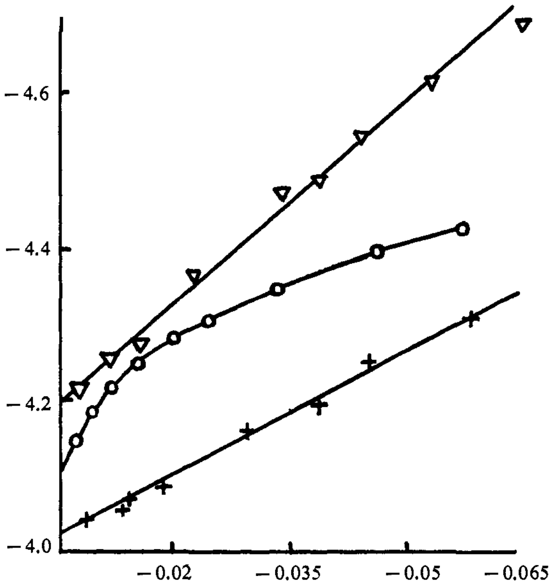


Figure 1. Determination of Bunnett's ω parameter for the hydration of mesityl oxide. Plot of (log k − H_0) *vs.* log a_{H_2O}: ▽, $HClO_4$; ○, HCl; +, H_2SO_4.

used to calculate Bunnett's parameters,[2] ω and ω*. The former is illustrated in Figure 1. Straight lines were obtained for H_2SO_4 (ω = 5.3) and $HClO_4$ (ω = 8.3), but for HCl the curvature is pronounced. In such cases it is recommended to evaluate ω* for which HCl gives a value of −3.0 as shown in Figure 2.

Table I. Summary of Kinetic Data

P, atm	$k \times 10^6$	ln k_p/k_1
Mesityl oxide (0.140 M) and HCl (0.490 M) in H_2O at 30°		
1	51 sec^{-1}	0
272	59	0.146
680	79	0.438
1088	95	0.622
1360	114	0.804
Mesityl oxide (0.105 M) and NH_3 (0.365 M) in H_2O at 30°		
1	132 l./mole sec	0
272	155	0.161
612	184	0.332
1088	247	0.627
1360	276	0.737
Mesityl oxide (0.070 M) and NH_3 (0.575 M) in MeOH at 30°		
1	25 l./mole sec	0
272	32	0.247
612	44	0.566
1088	64	0.940
1360	85	1.224
Mesityl oxide (0.100 M), PhSH (0.125 M), and NaOMe (0.025 M) in MeOH at 30°		
1	58 sec^{-1}	0
272	72	0.216
612	96	0.504
1088	140	0.881
1360	165	1.045
Mesityl oxide (0.100 M), PhSH (0.125 M), and NaOH (0.025 M) in EtOH-H_2O (55:45 by vol.) at 30°		
1	60 sec^{-1}	0
1088	137	0.826

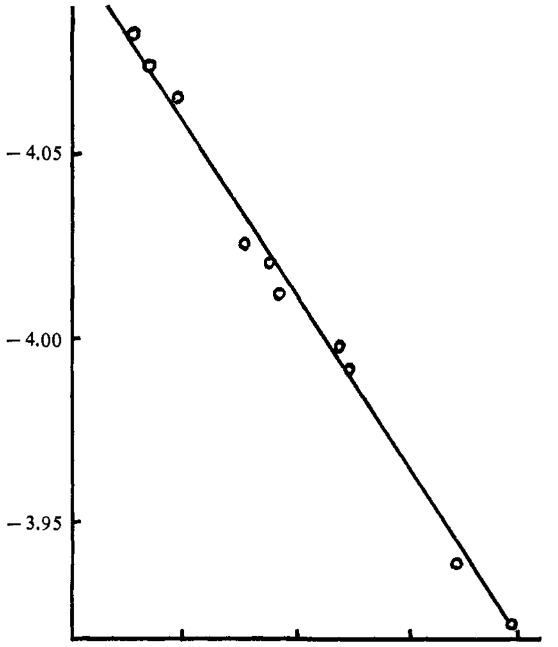


Figure 2. Determination of Bunnett's ω* parameter for the hydration of mesityl oxide. Plot of [log k − log (HCl)] against log a_{H_2O}.

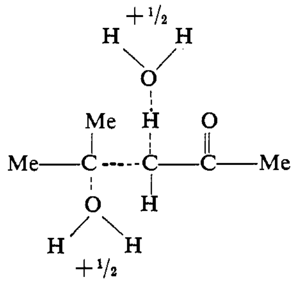
Bunnett's table correlating ω and ω* values with reaction mechanism is shown in Table II. It appears that the hydration of mesityl oxide proceeds by a concerted proton transfer and nucleophilic addition. This is in complete agreement with a transition state consisting of the aggregate (mesityl oxide, H^+, 2HOH) as deduced from the activation volume and the over-all volume of reaction.

Table II. Mechanistic Interpretation of ω and ω* Values

ω	ω*	Function of water in the rate-determining step
−2.5–0.0		Is not involved
1.2–3.3	<−2	Acts as a nucleophile
>3.3	<−2	Acts as a proton-transfer agent

Three conceivable transition states are illustrated below.

(i) Rate-determining proton transfer to the α-carbon



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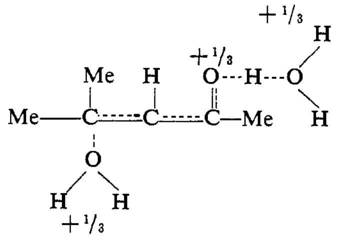
(ii) Rate-determining proton transfer to the carbonyl oxygen



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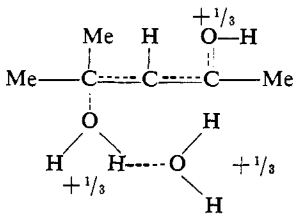
(iii) Rate-determining proton transfer at the oxygen of the attacking nucleophile, the substrate having been previously protonated



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It is not possible to discriminate among these mechanisms by using either activation volumes or Bunnett's parameters. Bell, Preston, and Whitney[3] proposed transition state **1** for this reaction with a rate-determining step the same as for enol–keto transformation. However, a termolecular mechanism with a transition state similar to **2** has been widely accepted for the hydration of acetaldehyde.[10]

Bunnett has suggested that the number of water molecules involved, that is, molecules of water able to affect reaction rates, can be correlated with ω values, one ω unit corresponding to one molecule of water. For this reaction ω values of 5 and 8 imply that 5–8 water molecules are involved, but the activation volume can be accounted for by only two molecules provided the interaction is strong. It is difficult to think of an operational test for the diffuseness of solvent participation in view of the fact that the water molecule oscillators are coupled by H bonding.

Acid-Catalyzed Addition of Methanol. The reversibility of the addition of methanol to mesityl oxide allows measurement of the effect of pressure on the equilibrium constant as well as the forward and reverse rates. The data are given in Table III. By plotting the logarithm of the equilibrium constant against pressure in accordance with the relation

$$RT(\partial \ln K/\partial P)_T = -\Delta V \qquad (1)$$

we obtain a value of -11 ml/mole for the volume of reaction. The same value was obtained by subtracting the sum of the molar volumes of methanol and mesityl oxide from that of 4-methoxy-4-methyl-2-pentanone. By direct measurement the activation volume is -23 ml/mole for the forward reaction and -13 ml/mole for the reverse. The difference should be equal to the volume of reaction according to the principle of microscopic reversibility, and the agreement is satisfactory.

It is worthy of note that the reverse (elimination) reaction cannot be a simple unimolecular decomposition of the conjugate acid of the ether in enolic form as shown below, else the activation volume would almost certainly be positive. The values of both the forward and reverse activation volumes point to a transition state containing two methoxy moieties and analogous in structure to **1**, **2**, or **3**.

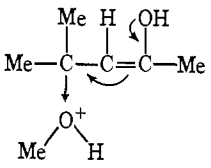

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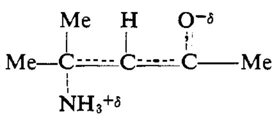
Table III. Kinetic and Equilibrium Data for Methanol–Mesityl Oxide System

P, atm	$k \times 10^6$, sec^{-1}	K, $c_{\text{product}}/c_{\text{reactant}}$
Mesityl oxide (0.035 M) and H_2SO_4 (0.050 M) at 30°		
1	26	1.49
272	34	1.69
612	46	1.95
1088	67	2.42
1360	91	2.77
4-Methoxy-4-methyl-2-pentanone (0.028 M) and H_2SO_4 (0.050 M) at 30°		
1	16	0.667
1088	28	0.416
	k_f/k_r	K, forward
1	1.62	1.49
1088	2.39	2.42

Addition of Ammonia. The kinetic data for this reaction are given in Table I. The volumes of activation were -14 ml/mole in water and -22 ml/mole in methanol. The volume of reaction, measured dilatometrically, was -9 ml/mole.

The variation of activation volume with solvent polarity indicates a polar transition state.



A dissection of the activation volume into separate components for solvent and reactant molecules may be attempted with the knowledge that the partial molar volumes of a variety of univalent electrolytes are 18–20 ml smaller in methanol or ethanol than in water.[11] If the relation between volume and polarization is assumed to be linear, the charge separation is 0.42 e; and if parabolic, 0.65 e. Since the volumes of ionization of acids and bases in water are about 25 ml/mole, the solvent component for our reaction in water would amount to $25 \times {}^{8}/_{19} = 10$ ml, leaving 4 ml to be accounted for by contraction of the reactants along the carbon–nitrogen bond axis. Recalling that the volume of reaction is -9 ml/mole, we may infer that the new bond of the transition state is approximately half-formed on both the geometrical and electrical scales.

Addition of Thiophenol. Thiophenoxide ion is the nucleophile for this addition, and reaction mixtures consisted of solutions of mesityl oxide, thiophenol, and sodium methoxide or hydroxide in the molar proportions 4:5:1. The kinetic data are given in Table I. The volume of activation was -20 ml/mole in methanol

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(10) Y. Pocker, *Proc. Chem. Soc.*, 17 (1960).

(11) S. D. Hamann and S. C. Lim, *Australian J. Chem.*, 7, 329 (1954).

and −19 ml/mole in a mixture of ethanol–water (55:45 by volume). A change in the amount of solvent electrostricted might have been expected since a negative charge is being transferred from the thiophenoxide ion to the carbonyl oxygen and therefore becomes somewhat dispersed. Since no significant change was observed we must ascribe the entire 19–20 ml to the formation of the carbon–sulfur bond. The volume of reaction observed in the dilatometer was −22 ml/mole, and it appears that the transition state lies very close to products on the reaction coordinate. If this is so, it is understandable that the activation volume showed no variation with solvent.

Experimental Section

Materials. Mesityl oxide and diacetone alcohol were prepared by the method of Vogel.[12] Mesityl oxide was distilled in the range 120–123° (648 mm). The methyl ether of diacetone alcohol was prepared by the method of Lorette[13] using Dowex 50 as an acid-exchange resin catalyst. Ammonia solution in methanol was prepared by heating a concentrated solution of ammonium hydroxide and passing the ammonia gas over calcium oxide and into methanol. The thiophenol was Eastman White Label grade. The methanol was Van Waters and Rogers 99.8% grade, and the ethanol was anhydrous U.S.P. reagent quality.

Dilatometry. The over-all volume changes were measured with a dilatometer of 17.5 capacity with a capillary of 1 mm. The dilatometer was weighed before and after the reaction period to ensure that volume changes were not caused by evaporative loss. The volumes of mixing of mesityl oxide and diacetone alcohol with water were determined by measuring the densities of the pure components and the density of the mixture. Concentrations used were the same as those used in the determination of the volume of activation since volumes of mixing are somewhat dependent on concentration.

Methods of Kinetic Measurement. Addition of water, methanol, and ammonia were followed by the disappearance of mesityl oxide which was determined spectrophotometrically[3] employing the absorption peak at 243 mμ for which $\epsilon = 1.10 \times 10^4$. A Beckman Model DU spectrophotometer, using a hydrogen lamp as an ultraviolet light source, was employed for absorbance measurements.

Rate constants for the addition of water were determined from a plot of the logarithm of concentration of mesityl oxide against time. Both forward and reverse rate constants for the addition of methanol were determined from the expressions

$$K = k_f/k_r \qquad (2)$$

$$\ln (c_0 - c_\infty)/(c - c_\infty) = k_f[c_0 t/(c_0 - c_\infty)] \qquad (3)$$

which is the solution of the rate equation

$$\mathrm{d}c/\mathrm{d}t = -k_f c - k_r(c_0 - c) \qquad (4)$$

where c_0 = initial concentration of mesityl oxide, c_∞ = equilibrium concentration of mesityl oxide, and c = concentration of mesityl oxide at time t. Equilibrium constants at various pressures were determined from the ratio of the percentage of mesityl oxide converted to the percentage remaining.

The second-order rate constants for the addition of ammonia were determined from the expression

$$1/(b - a) \ln [a(b - x)/b(a - x)] = kt \qquad (5)$$

which is the solution of the rate equation

$$\mathrm{d}x/\mathrm{d}t = k(a - x)(b - x) \qquad (6)$$

where x = decrease in concentration of mesityl oxide, a = initial concentration of mesityl oxide, and b = initial concentration of ammonia. Kinetic data for this addition were obtained from solutions that had reacted up to 40% completion. The reverse reaction was disregarded due to the high percentage conversion (88%) at equilibrium.

Rate constants for the addition of thiophenol were determined from a plot of the logarithm of concentration of mesityl oxide against time. The mesityl oxide concentration was obtained from the relation

$$c_{\mathrm{mo}} = c^0{}_{\mathrm{mo}} - (c^0{}_{\mathrm{SH}} - c_{\mathrm{SH}}) \qquad (7)$$

where $c^0{}_{\mathrm{SH}}$ is the initial titratable thiophenol (includes thiophenoxide) concentration and c_{SH} is the titratable thiophenol at time t.

Titrations were done potentiometrically with a Beckman Zeromatic pH meter, using a silver electrode, against a standard silver nitrate solution. The initial mesityl oxide concentration was determined spectrophotometrically. The rate constant obtained is pseudo first order and includes the thiophenoxide concentration term which remains constant

$$\mathrm{d}(c_{\mathrm{SH}})/\mathrm{d}t = kc_{\mathrm{mo}}c_{\mathrm{S^-}} \qquad (8)$$

$$= k'c_{\mathrm{mo}} \qquad (9)$$

Sampling Technique. The sampling technique was basically the same for all the addition reactions. Aliquots totalling 5 ml were pipetted into a 6-ml, narrow-necked test tube, and mercury was added so that the solution filled the test tube. The tube was then inverted into a larger test tube; the two tubes were sealed by adding more mercury, and the larger one was filled with water and placed in the pressure vessel. After a suitable reaction time, usually longer than 3 hr, a 3-ml aliquot was removed for analysis. Considerable dilution was necessary for the determination of mesityl oxide concentrations spectrophotometrically owing to its very large extinction coefficient at 243 mμ. Dilutions were adjusted so that absorbance measurements of around 0.500 were obtained.

Experimental Error. The error in the volume of activation is due almost entirely to the uncertainty in the term $\ln k_p/k_1$. From duplicate rate measurements this uncertainty is from 4 to 8% and hence activation volumes obtained are accurate within the range of ±1.0 to ±1.6 ml/mole. Temperatures were controlled to within 0.05° and pressures within 7 atm. Uncertainty in the reaction time was rendered negligible by having sufficiently long reaction times, usually from 3 to 4 hr. From duplicate measurements the uncertainty in the over-all volume changes is about 5%.

Calculation of Activation Volumes. The logarithm of the ratio of the rate constant at pressure to the rate constant at 1 atm (k_p/k_1) was plotted against pressure, and the best straight line was drawn through the origin and the other points. The slope was used to evaluate the activation volume according to the equation

$$RT(\partial \ln k/\partial P)_T = -\Delta V^* \qquad (10)$$

None of the plots had any obvious curvature, and this seems surprising in only one case, the addition of ammonia with methanol as solvent. Ion-producing reactions in organic solvents often show curvature at pressures as low as 1000 atm.[4]

Acknowledgment. The authors are indebted to the National Science Foundation which supported this work through Grant GP-1718.

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[12] A. I. Vogel, "A Textbook of Practical Organic Chemistry," 3rd ed, Longmans, Green, and Co., London, 1961, pp 351–353.

[13] N. B. Lorette, *J. Org. Chem.*, **23**, 937 (1958).