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THE EFFECT OF PRESSURE ON STERICALLY HINDERED MENSHUTKIN REACTIONS[1a,b]

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Abstract—A systematic study is described of the effect of pressure on the rates of the Menshutkin reactions of pyridine and various 2,6-dialkylpyridines with methyl, ethyl, and isopropyl iodide. A general increase of the pressure-induced acceleration of the rates with steric hindrance has been found. The magnitude of the effect does not appear to be solvent dependent, which lends strength to the interpretation advanced by Gonikberg that this effect is primarily due to the interpenetration of interfering groups.

THE effect of pressure on a rate constant, usually measured over a range of 0 to 1–10 kbar, allows one to calculate the activation volume of the reaction by means of the expression:

$$\left(\frac{\partial \ln k}{\partial p}\right)_T = -\frac{\Delta V^*}{RT}$$

where k is expressed in concentration units at 1 atm.[3] ΔV^* is typically found to be in the range of +20 to −20 cm^3/mole, and since $R = 0{\cdot}083$ cm^3 kbar/mole °K, the effect of pressure on k will correspondingly be a factor of 0·5 to 2 for each kbar. ΔV^* is not independent of the pressure but tends to zero at very high pressures. Since most chemists are primarily interested in data that apply under room conditions of pressure as well as temperature, the quantity reported is usually ΔV_0^*; the slope $\partial \ln k/\partial p$ is evaluated by means of the expression $\ln k = ap^2 + bp + c$.[4] The value of ΔV_0^* is that it can be predicted for most mechanisms with fair accuracy, on the basis of (a) comparisons with pressure data for reactions of well-known mechanism; (b) volume changes in equilibria; and (c) densities and parachor data of stable substances. This ability allows one to use the pressure coefficient of a rate constant as a mechanistic criterion in many cases.

Several features make important contributions to ΔV_0^*. Bond formation seems to be characterized by a volume change of −5 to −10 cm^3/mole, while bond cleavage has the opposite effect. Displacements in which there is no net change in the number of charges also have small negative volumes of activation, suggesting that bond formation is more advanced in the transition state than the concurrent bond fission. Ionization is characterized by the rather large overall contraction of −15 to −30 cm^3/mole, which is considered to be due to the attraction of surrounding solvent molecules by the newly formed charges (electrostriction). By the same token, charge neutralization causes solvent relaxation and expansion. Smaller changes in volume can sometimes be attributed to changes in shape, to charge delocalization and bond deformation. Almost all reactions can be considered to be summations of these various factors. The solvent and temperature have also been found to affect ΔV^* in many cases.

One serious attempt has been made by Eyring to put estimates of ΔV^* on a semi-theoretical basis.[5] These calculations were founded on the assumptions, first, of a simple geometric shape for the reactant(s) and the transition state, and second, of transition bond lengths 10% greater than normal bond lengths. The latter assumption[6] proved to be popular and it survives in many discussions to this day, even though there is now much information available showing that the 10% bond lengthening is usually a gross underestimate.[7] Solvation contributions were not considered. Eyring[5] applied this method to the reactions for which ΔV^* was then known and obtained amazingly good agreement in most cases. However, this general agreement should be considered fortuitious as many of these reactions are now known to go by complex pathways; others are now known to have activation volumes greatly affected by solvent, and still others with better experimental work were subsequently found to have activation volumes very different from the earlier values.

A factor of great potential interest is that of steric hindrance. Crowded compounds usually have somewhat greater densities than their unhindered isomers, and it would seem reasonable to suppose that hindered transition states would similarly have smaller volume requirements than the unhindered substrates from which they may be formed. If this is so, hindered reactions should be accelerated to a greater degree than their unhindered analogs—clearly a possibility of much interest. Evidence for it has been reported by several groups. The first claim was made by Perrin,[8] who noted in 1937 that the pressure induced acceleration of the reaction of pyridine with alkyl iodides at 60° increased in the order methyl < ethyl < i-propyl, and concluded: "... variations in the numerical values of the acceleration may be due to the forcing together of the molecules so that steric restrictions may be more easily overcome."

Major contributions have been made to this question by Gonikberg and his co-workers. They found[9] that while the activation volumes for the reactions of methyl iodide with pyridine and with 4-picoline under similar conditions differ by only 0·5 cm^3/mole, ΔV_0^* for the reaction of 2,6-lutidine is 3·4 cm^3/mole more negative than that of pyridine itself, and the reaction of the lutidine with i-propyl iodide has a ΔV_0^* more negative by 6·7 cm^3/mole than that of pyridine with ethyl iodide. In other examples they have found[10] that 2,4-dinitrochlorobenzene reacts with n-butylamine and with t-butylamine with activation volumes of $-31{\cdot}0$ and $-35{\cdot}0$ cm^3/mole, respectively; that in the homolytic phenylation of t-butylbenzene[10] the *o*/*p*-ratio increases from 0·63 to 1·20 between 1 and 6000 atm, and that pressure favors the incorporation of tetrachloroethylene in copolymerization with vinyl acetate more than that of trichloroethylene.[11] Gonikberg concluded in several of these papers that "the more sterically hindered a chemical reaction, the greater the degree to which it should be accelerated with increasing pressure", and wrote in 1967 that if one considers a reaction in which a sterically hindered product accounts for only 10% of the product, if the ΔV^* of its formation is 10 cm^3/mole smaller (or more negative) than that of its unhindered competitor, then it may dominate to the extent of 75% at 30 kbar.[12] This estimate was based on the admittedly dubious assumption that $\Delta\Delta V^*$ would be independent of the pressure.

Weale similarly found several remarkable instances of pressure effects on sterically hindered reactions. The reactions of methyl, ethyl and i-propyl iodides with N,N-dimethylaniline in methanol at 25° are characterized by activation volumes of −26, −34 and −47 cm^3/mole, respectively, and that of ethyl iodide with N,N-dimethylbenzylamine has a ΔV^* of −27 cm^3/mole.[13] Recently, Okamoto studied some extreme examples. The reaction of methyl iodide with 2,6-di-t-butylpyridine, which does not occur at atmospheric pressure at all, was reported readily to afford the N-methyl iodide at 5 kbar;[14] the reaction of 2,4,6-tri-t-butyl-N-methylaniline with methyl iodide, which does not occur at atmospheric pressure, gives 2,4-di-t-butyl-N,N-dimethylaniline iodide at high pressure—apparently via an initial Menshutkin reaction,[14] and he found other examples of this sort.[15]

In spite of this evidence,[16] it is probably still too early for a generalization such as was proposed by Gonikberg. For one thing, almost all of the examples that have been found are Menshutkin reactions, and even in that reaction the evidence is more apparent than real since one must often compare data gathered in different solvents, at different temperatures and over different pressure ranges. Secondly, while it is true that crowded compounds are more dense than their unhindered isomers, the differences in molar volume seem rarely to be more than a cm^3 or two; but the $\Delta\Delta V^*$-values reported are often much larger than that. The effects reported by Okamoto seem to be much larger still—larger than can be accommodated by any of the theories yet offered.

The potential of this phenomenon—a selective increase of the rate of sterically hindered reactions—appeared to us great enough to warrant a systematic investigation. The present work was carried out with the objective of providing directly comparable data for a number of Menshutkin reactions, all studied in the same solvent, at the same temperature and over the same pressure range, but with widely different steric requirements.

RESULTS AND DISCUSSION

The results of the Menshutkin reactions are summarized in Table 1.

Even though we used only three measurements to compute the second order rate constants in most cases (more if these did not lie on a straight line), our results compare well with the literature values where these are available. For instance, for pyridine and methyl iodide we find k_2-values of 30·9 and 60·8 × 10^{-5} l/mole sec in acetone at 30 and 40°, respectively; for these conditions Hartmann[17] reported 31·0 and 61·6 × 10^{-5} l/mole sec. Hartmann's activation volumes are nevertheless more negative than ours (e.g. −28·8 cm^3/mole for this reaction in acetone at 50°). This is due in part to the higher temperature, partly due to a difference in computation (his data with our program yield −26·9 cm^3/mole), and partly to his narrower range of pressures (see above; a graph shows his data below 1 kbar and ours above that pressure to lie on a single smooth curve). Gonikberg's value for pyridine and ethyl iodide[18] is also more negative than ours (−30 at 40°) and for the same reasons; however, since we are primarily concerned with *differences* between the various ΔV^*-values, we need not further concern ourselves with the absolute values.

TABLE 1. RATE CONSTANTS[a] AND ACTIVATION VOLUMES[b] OF VARIOUS MENSHUTKIN REACTIONS IN ACETONE AT 25°

R'I 2,6-di-R-C_5H_3N Pressure, kbar	Me H 10^4k	Me Me 10^5k	Me Et 10^6k	Me i-Pr 10^7k	Me t-Bu 10^8k[c]	Et H 10^5k	Et Me 10^7k	Et Et 10^8k	Et i-Pr 10^8k	i-Pr H 10^7k	i-Pr Me 10^9k
0·001	2·14	0·60	0·79	0·32	—	1·10	0·78	0·65	—	3·36	1·17
0·689	4·10	1·40	1·82	0·86	—	2·40	1·53	1·89	—	7·22	2·84
1·379	6·04	2·31	3·45	1·73	—	3·64	2·78	3·18	—	15·5	5·54
2·758	15·2	5·91	8·85	4·33	—	9·16	7·32	8·81	—	35·7	11·9
4·137	32·4	11·4	17·8	8·21	0·75	18·4	17·1	18·4	1·08	66·7	26·5
5·516	44·8	20·4	28·2	12·3	7·5	27·8	31·7	32·8	2·33	115	32·3
ΔV_0^*	−21·9	−24·4	−27·3	−30·2	< −50	−23·3	−23·9	−28·3	−35	−26·5	−28·2

[a] In l/mole, sec.

[b] In cm^3/mole; the correlation coefficients exceeded 0·997 in all cases

[c] At 56°; not a Menshutkin reaction (see text)

Our results show a regular increase in the absolute value of ΔV^* with increasing substitution; the change is approximately 2–3 cm^3/mole with every additional carbon atom in the alkylating agent, and with every additional carbon atom substituted on the α-carbon of the 2- and 6-side chains. Two results deserve comment.

The reaction of ethyl iodide with 2,6-diisopropylpyridine is so slow at ordinary pressures that we were unable to measure the rate constant, and could do so only at pressures of 4–5 kbar; thus, this reaction joins a number found by Okamoto that can be said to occur only at high pressures. The crude estimate of -35 ± 3 cm^3/mole for ΔV_0^* is based on these two data and on a comparison with our data in the same pressure range for the faster reactions.[19] The acceleration by pressure of the reaction of methyl iodide with 2,6-di-t-butylpyridine similarly proved measurable only at pressures in the upper range, and even there the acceleration is still enormous, leading to an estimated absolute value for ΔV^* far more negative than -50 cm^3/mole. As had been pointed out earlier,[3] this value cannot be accounted for even if the methyl group simply vanished between the t-butyl groups. It had also been reported that the quaternary salt isolated had some unexpected properties; thus, in spite of the strain to be expected the salt could be sublimed unchanged at 250°.[14] For these reasons we reexamined the identity of the product. The N-Me peak was absent in the NMR-spectrum, and in all its properties the material proved to be identical with the hydrogen iodide prepared at 1 atm from the pyridine and aqueous HI.† It is of course possible that the ΔV^* estimated as noted on the basis of two high pressure rate constants is in fact that of the Menshutkin reaction, and that the decomposition to the hydrogen iodide is a fast step following the rate limiting one; however, this is only conjecture at the moment.

Two explanations for the effect of pressure on steric hindrance have been advanced, both primarily in connection with the Menshutkin reaction. Gonikberg's is essentially an extension of the Eyring method described earlier. It is assumed that the C—N bond is 10% longer in the transition state than in the final product; electrostriction is ignored, and the steric effect is attributed to "overlapping volumes", or

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† Professor Okamoto has informed us that he agrees the former structure assignment was in error.

"interpenetration of orbitals". In other words, the ortho-substituents and the groups attached to nitrogen in the transition state to some degree use the same space. By means of some simplifying assumptions Gonikberg was able to calculate the magnitude of this space, and arrived at numbers amazingly close to those observed. On the other hand, Hamann[20] and Weale[21] have criticized this approach because of the arbitrary assumption of the CN bond length in the transition state, and because the volume of activation of the Menshutkin reaction is so sensitive to solvent that it seems unreasonable not to attribute some role to the solvent in the steric effect. Thus, Hartmann[17] found ΔV_0^* for the reaction of pyridine with methyl iodide at 50° to be -19.7 cm^3/mole in nitrobenzene, -28.8 cm^3/mole in acetone, and -33.9 cm^3/mole in carbon tetrachloride. One could imagine that the role of the alkyl substituents is effectively to change the medium in the immediate surroundings of the reaction center to a rather non-polar one, and that ΔV_0^* becomes more negative as a result of that. Brower[22] has devised an ingenius approach to this kind of question, which consists of measuring ΔV^* in a series of solvents covering a range of polarities. The bonding contribution to ΔV_0^* should be independent of the solvent, whereas the charge-solvent interaction should obviously not be. We are now in a position to comment on the objection of Hamann and Weale. Gonikberg's ΔV_0^* data were measured in nitrobenzene, a solvent in which such values for the Menshutkin reaction tend to be small, and ours were determined in acetone, a medium in which ΔV_0^* tends to be large. A comparison of his results[16b] with ours shows that $\Delta\Delta V^*$ in acetone is certainly not larger than in nitrobenzene, and hence that solvation may be neglected in determining the *difference* in pressure effects on the rates of various substituted pyridines (though not in determining the effects themselves, as was done by Gonikberg *et al*).

We conclude that the correlation between steric hindrance and increased pressure induced rate accelerations, previously noted on the basis of some isolated or incomparable data, does indeed exist in the case of the Menshutkin reaction; and that Gonikberg's explanation of this effect is supported by the absence of a solvent effect on this correlation; but whether the effect can be safely extended to other reactions remains to be seen.

EXPERIMENTAL

The purifications of Me,[23] Et,[23] and i-Pr[24] iodide have been described. Pyridine and 2,6-lutidine were obtained from commercial sources and distilled from KOH pellets. 2,6-Diethyl-,[25] diisopropyl-[26] and di-t-butylpyridine[27] were prepared by known methods. VPC and NMR were used in all cases to ensure a high degree of purity. Acetone was stirred with anhyd K_2CO_3 for 3 days and then distilled from a mixture of Drierite and $KMnO_4$ with a reflux ratio of 10; the water content was shown by NMR to be considerably less than 0·1 %. In the kinetics experiments, equimolar amounts of both reagents were used; the concentrations used varied with the rates of the reaction. The reaction was quenched by the addition of cold water and the resulting mixture was immediately titrated with $AgNO_3$ aq. In the faster reactions, the Volhard procedure was employed with 0·1 M $AgNO_3$; in the slower reactions, 0·01–0·005 M $AgNO_3$ was used in a potentiometric analysis. The temp was maintained at 25·00 ±0·05° in all cases except in that involving the 2,6-di-t-butylpyridine as noted (56°). The high pressure apparatus was used as described previously.[3]

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