

SOLVENT ISOTOPE EFFECT ON NUCLEOPHILIC ATTACK OF METHOXIDE ION AND HYDROXIDE ION ON sp^2 CARBON ATOM OF *trans*-3-METHOXY- OR *trans*-3-METHYLTHIO-ACRYLOPHENONES

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SUMMARY

The second-order rate constants for the base-catalysed reactions of methanol with 3-methoxy- and 3-methylthio-acrylophenones (MeOAcr and MeSAcr) have been determined in methanol and in methanol-OD at 25°C. Non-catalytic terms were not detected. Inverse kinetic solvent isotope effects on attack of methoxide ion on MeOAcr and MeSAcr of 0.62 and 0.57, respectively, are compared with earlier data for attack of methoxide ion on a substituted *N*-benzylideneaniline. The rate constants depend on electrophiles, but the solvent isotope effects, ca. 0.6, are fairly constant, irrespective of the 10^4 fold variance of the rate constants. The results are discussed in terms of solvent reorganisation. The solvent isotope effect for the reaction of hydroxide ion in water was also determined.

Reaction rates of a number of nucleophiles with *trans*-3-methoxyacrylophenone (MeOAcr) and with *trans*-3-(methylthio)-acrylophenone (MeSAcr) in water and in methanol were reported.¹ The rate-determining step of the reaction of methoxide ion with MeOAcr and MeSAcr is believed to be attack of methoxide ion.¹ This situation is very similar to that for methoxide ion-catalysed addition of methanol and propanethiol across the C=N double bond of *N*-(substituted)-benzylideneaniline,^{2,3} in which inverse kinetic solvent isotope effects were observed.

Kinetic solvent isotope effect is one of the useful criteria for the determination of the rate-determining step of the reaction including proton transfer step.⁴ Though solvent isotope effects on specific base-catalysed reactions in water have extensively studied, only a few solvent isotope effects in methanol have been reported for the specific base-catalysed reactions^{2,3,5} including methanolysis of aryl esters.⁶⁻⁸ To obtain more information of the rate-determining step and to compare these reactions for MeOAcr and MeSAcr with the ones for *N*-benzylideneanilines, kinetic solvent isotope effects for the

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Table 1. FIRST ORDER RATE CONSTANTS FOR THE REACTION OF METHOXIDE ION WITH MeOAcr AND MeSAcr IN METHANOL AT 25^a

Substrate	Solvent	[MeO ⁻]/M	$k_{\text{obs}}/\text{s}^{-1}$
MeOAcr	MeOH	0.0086	0.0102
		0.0122	0.0148
		0.0172	0.0202
		0.0183	0.0225
		0.0183	0.0234
		0.0244	0.0308
		0.0258	0.0305
		0.0305	0.0344
	MeOD	0.0061	0.0118
		0.0122	0.0238
		0.0153	0.0314
		0.0183	0.0354
		0.0244	0.0478
		0.0305	0.0588
MeSAcr	MeOH	0.0305	1.02×10^{-4}
		0.0457	1.50×10^{-4}
		0.061	2.18×10^{-4}
	MeOD	0.0305	1.83×10^{-4}
		0.0457	2.68×10^{-4}
		0.061	3.62×10^{-4}

^a Initial concentrations [MeOAcr]₀ = 2.0×10^{-4} M ;
[MeSAcr]₀ = 1.0×10^{-4} M

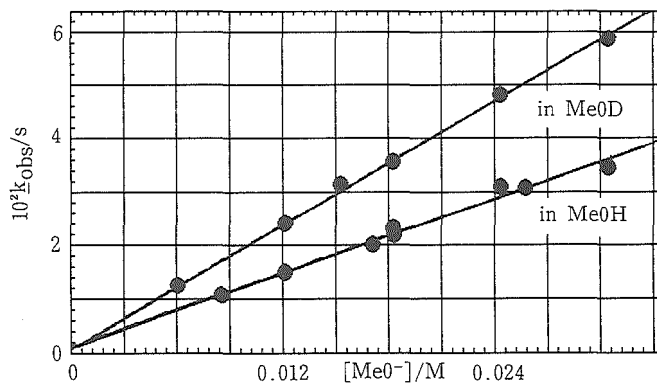


Figure 1 First order dependence of the first order rate coefficients on methoxide ion concentrations for the reaction of methoxide ion with 3-methoxyacrylophenone.

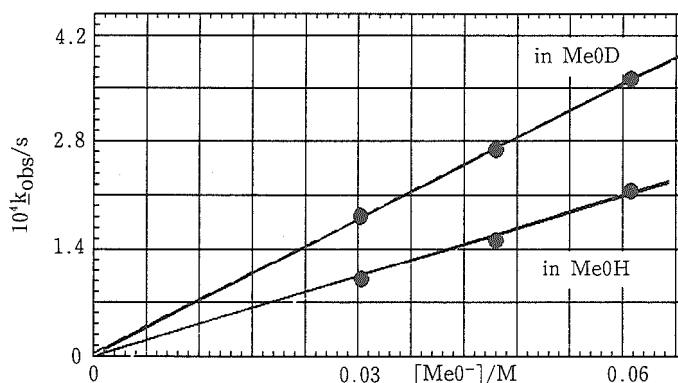


Figure 2 First order dependence of the first order rate coefficients on methoxide ion concentrations for the reaction of methoxide ion with 3-methylthioacrylophenone.

reactions of methoxide ion with MeOAc and MeSAc in methanol at 25.0°C have been measured and presented here.

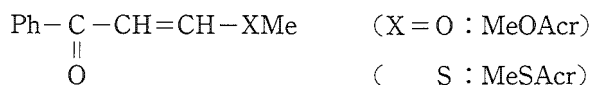


Table 2. KINETIC SOLVENT ISOTOPE EFFECTS FOR THE ATTACK OF METHOXIDE ION ON sp^2 CARBON ATOMS AT 25°

Substrate	Nucleophile	Solvent	$k_2/M^{-1} s^{-1}$	SIE
PhCOCH=CHOMe ^a	MeO ⁻	MeOH	1.21 ± 0.05	
	MeO ⁻	MeOD	1.96 ± 0.04	0.62
PhCOCH=CHSMe ^a	MeO ⁻	MeOH	3.41 ± 0.06 × 10 ⁻³	
	MeO ⁻	MeOD	5.94 ± 0.05 × 10 ⁻³	0.57
<i>p</i> -NO ₂ C ₆ H ₄ CH=NC ₆ H ₄ Cl- <i>m</i> ^b	MeO ⁻	MeOH	2.35 × 10 ⁻⁴	
	MeO ⁻	MeOD	3.9 × 10 ⁻⁴	0.60
<i>p</i> -NO ₂ C ₆ H ₄ CH=NC ₆ H ₄ Cl- <i>m</i> ^c	PrS ⁻	MeOH	2.22 × 10 ⁻²	
	PrS ⁻	MeOD	2.82 × 10 ⁻²	0.56
PhCOCH=CHOMe ^a	HO ⁻	H ₂ O	0.427	
	DO ⁻	D ₂ O	0.486	0.88
PhCH=NOH ^d	HO ⁻	H ₂ O	3.03	
	DO ⁻	D ₂ O	4.23	0.72

^a This work

^b Y. Ogata and A. Kawasaki, *J. Org. Chem.*, **39**, 1058 (1974).

^c Y. Ogata and A. Kawasaki, *J. Chem. Soc.*, Perkin Trans. 2, 134 (1975). Estimated value on assuming the solvent isotope effect on the dissociation of propanethiol, $K_a(\text{MeOH})/K_a(\text{MeOD}) = 2.5$.

^d A. Williams and M. L. Bender, *J. Amer. Chem. Soc.*, **88**, 2508 (1966).

Results and Discussions

Reaction of Methoxide Ion. The reactions were spectrophotometrically clean simple additions of methanol across the double bonds, and followed good pseudo-first-order kinetics as reported earlier.¹ The apparent first order rate constants in methanol and methanol-OD in Table 1, showed excellent first order dependence on the methoxide ion concentrations, as shown in Figures 1 and 2. The correlation coefficients r 's are between 0.991 and 1.000. The intercept, the uncatalysed rate constant, is zero or negligibly small. This is consistent with the earlier observation that the reaction with methanol does not proceed appreciably without base. The observed second order rate constants, shown in Table 2, were obtained from the linear least square method and precise to better than 5%. If the original points ($k_{obs}=0 \text{ M}^{-1} \text{ s}^{-1}$ without base) are included, the correlation coefficients between k_{obs} and $[\text{MeO}^-]$ are much improved. The rate constants, k_2 , intercepts, and correlation coefficients are: 1.17, 5.4×10^{-4} , 0.995 for MeOAc in methanol; 1.94, 2.99×10^{-4} , 0.999 for MeOAc in methanol-OD, SIE=0.60; 3.51×10^{-3} , 2.97×10^{-6} , 0.998 for MeSAc in methanol; 5.91×10^{-3} , 4.43×10^{-7} , 1.000 for MeSAc in methanol-OD, SIE=0.59, respectively. The rate constants in methanol are consistent with the earlier values¹ within experimental errors (10%).

Reactions of Hydroxide Ion. The reaction of hydroxide ion with MeOAc produced the enolate ion of benzoyl-formaldehyde. Following retro-aldol reaction of this enolate was negligibly small under the present conditions, as described in earlier paper.¹ The observed pseudo-first-order rate constants were precise to better than 5% and are shown in Table 3. The second order rate constants, obtained by the division of the

Table 3. RATE CONSTANTS FOR THE REACTION OF HYDROXIDE ION WITH MeOAc IN AN AQUEOUS SOLUTION AT 25^a

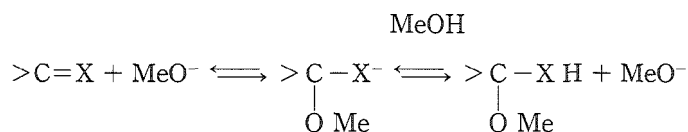
Solvent	$[\text{OH}^-]$ or $[\text{OD}^-]/\text{M}$	k_{obs}/s^{-1}
H ₂ O	0.0156	0.0068
	0.0312	0.0134
	0.0312	0.0139
	0.0468	0.0189
	0.0624	0.0246
	0.0624	0.0281
D ₂ O	0.0156	0.0086
	0.0312	0.0151
	0.0312	0.0149
	0.0468	0.0221
	0.0624	0.0297
	0.0624	0.0283

^a Initial concentrations $[\text{MeOAc}]_0 = 2.0 \times 10^{-4} \text{ M}$

first-order rate constants with the concentration of hydroxide ions, are $0.49 \pm 0.03 \text{ M}^{-1} \text{ s}^{-1}$ for OD^- reaction in D_2O and $0.43 \pm 0.02 \text{ M}^{-1} \text{ s}^{-1}$ for OH^- in H_2O , respectively. Therefore, the solvent isotope effect, $k^{\text{H}_2\text{O}}/k^{\text{D}_2\text{O}}$, is 0.88. This is consistent with a mechanism involving rate-determining attack by hydroxide ion on the unsaturated carbon atom.

Deuterium Solvent Isotope Effect. As seen from Table 2, deuterium solvent isotope effects (0.62 and 0.57) for the reaction of methoxide ion with MeOAc and MeSAc are compared with the earlier data (0.60) for the base-catalysed addition of methanol to *N*-(*p*-nitrobenzylidene)-*m*-chloroaniline.² The comparison of the data implies at least two points. First the observation of inverse isotope effect indicates that the rate-determining step is surely attack of methoxide ion on the acrylophenones. If the following protonation were rate-determining step, a kinetic isotope effect over unity could be observed. This is not the case. Besides, the coincidence of the present isotope effects with the earlier data indicate that same mechanism (Scheme I) should be exerted for those reactions.

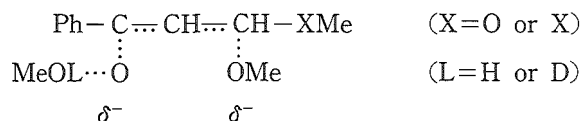
Scheme I



Second, the solvent isotope effect for attack of methoxide ion on the carbon atom of sp^2 hybridisation in methanol is constantly 0.6, irrespective of 10^4 fold variance of the rate constants from 1 to $10^{-4} \text{ M}^{-1} \text{ s}^{-1}$. The variance can be related to that of electrophile reactivities, while the change of the rate constants with change of isotope solvent can be related to the methoxide ion reactivity. The concentrations of methoxide ion in methanol and methanol-OD are essentially same. Since acidity of methanol is higher than that of methanol-OD, methoxide ion is more reactive in methanol-OD than in protiated methanol. Therefore, desolvation of methoxide ion is easier in methanol-OD.

The solvation of the probable transition state or general acid catalysis (II) should be stronger in methanol, and therefore the reaction rate should be higher in a protiated solvent. If it were important, a kinetic isotope effect over unity would be expected, which is not the case.

Scheme II

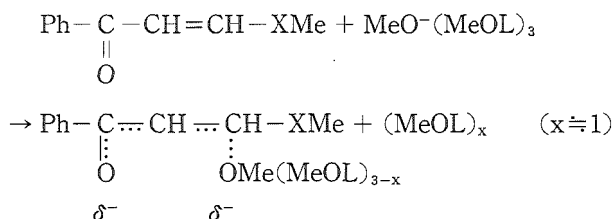


In conclusion, desolvation of the reagent methoxide ion is the most important factor that controls reaction rate in changing solvent. This is consistent with Ritchie's suggestion of the importance of solvent reorganisation before reactions⁹.

According to Wong and Schowen's model⁵, the value of $k^{\text{MeOD}}/k^{\text{MeOH}}$ for the liberation

of a molecule of methanol solvation for the reaction of methoxide ion is about 1.4 ($=1/0.74$) and that of two molecules is about 2.0 ($=1/0.74^2$). Here the solvation number is assumed to be 3 for methoxide ion and the average fractionation factor to be 0.74 for a methanol molecule toward methoxide ion¹⁰. The present solvent isotope effects, $k^{\text{MeOD}}/k^{\text{MeOH}}$, are 1.6 for MeOAc and 1.7 for MeSAc, respectively. These correspond to the loss of more than a molecule of methanol solvation in the transition state (Scheme III).

Scheme III



Experimental

Preparations of *trans*-3-methoxy- and *trans*-3-methylthioacrylophenones were described previously.¹ Preparations of all other materials, reagents and solvents have also been described in earlier papers.^{1,2} Methanol-OD of over 99% was purchased commercially. Reactions were followed under pseudo-first-order conditions, monitored spectrophotometrically on a Shimadzu Model UV-300 spectrophotometer of which cell compartment was thermostated at 25.0°. Second-order rate constants were obtained from the plot of the pseudo-first-order rate coefficients vs the concentration of KOH in methanol or methanol-OD. The procedure has been described earlier.¹

Acknowledgements

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