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Effects of Alkali Metal Cation, Solvent, and Alkylating Agent on the Alkylation of Alkali Metal Enolates of Ethyl Acetoacetate

Yoshinori Hara and Minoru Matsuda

Chemical Research Institute of Non-aqueous Solutions, Tohoku University, Katahira 2-Chome, Sendai 980

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Alkylation of Li^+, Na^+, and K^+ enolates of ethyl acetoacetate by dimethyl sulfite in dimethyl sulfoxide, hexamethylphosphoric triamide, and *N,N*-dimethylformamide at 50 °C has been studied. The ratio of O/(C+C,C)-alkylation is considerably dependent on the size of the counter cation and the solvent. The tightness of the ion pair is responsible for determining the ratio. The structure of alkylating agents has also influence upon the alkylation ratio. Dimethyl sulfite gives a higher O/(C+C,C)-alkylation ratio than methyl halides which may be ascribed to the hard methyl sulfite anion as leaving group.

It seems to be of interest to determine the factors affecting the alkylation site of ambident anions such as alkali metal enolates of ethyl acetoacetate. Several studies of this area have revealed that the ratio of O/(C+C,C) in alkylation reactions is remarkably dependent on the structure of the alkylating agents, the size of the metal cations, the solvent, and the temperature.[1-6] In connection with our previous studies concerned with the syntheses of organic compounds having sulfite linkages,[7,8] our attention has been focused on the use of dimethyl sulfite in organic reactions in order to understand the chemical properties of the relatively less known alkyl sulfite as alkylating agent.[9] We will report here the alkylation reaction of the alkali metal enolates of ethyl acetoacetate by dimethyl sulfite and the results are discussed in terms of the effects of the size of alkali metal cations, the solvent, and the alkylating agent.

Results

Solvent Effects on the Isomer Ratio in Alkylation Reaction. Results obtained from alkylation of sodium enolate of ethyl acetoacetate by dimethyl sulfite in several solvents at 50 °C are listed in Table 1. The O/(C+C,C)-alkylation ratio increases in the order of diglyme< *N,N*-dimethylformamide (DMF)<dimethyl sulfoxide (DMSO)<hexamethylphosphoric triamide (HMPA)< liquid SO_2. Reaction in liquid SO_2 proceeds in a heterogeneous system. The yield of C,O-isomers is negligibly small.

Counter Cation Effects. Results obtained in DMSO at 50 °C are listed in Table 2. The O/(C+C,C)-alkylation ratio increases in the order of Li^+<Na^+<K^+

Table 1. Alkylation of sodium enolate of ethyl acetoacetate by dimethyl sulfite in various solvents[a)]

Solvent	Reaction time (h)	Total yield (mol%)	Products (mol%)			Donicity number	Dielectric constant
			C-isomer	C,C-isomer	O-isomer		
HMPA	48	50	37	2	61	38.8	30
DMSO	44	50	53	1	46	29.8	~45
DMF	44	42	54	2	44	30.9	35
DMSO (70 vol. %) —*t*-BuOH	46	51	58	2	40		
Diglyme[b)]	48	19	66	~0	34		
liquid SO_2[c)]	48	18	13	<1	86		

a) [Enolate]=1.0 mol/l. b) [Enolate]=0.25 mol/l. c) Heterogeneous.

Table 2. Methylation of the alkali metal enolates of ethyl acetoacetate by various alkylating agents at 50 °C[a)]

Alkylating agent	Alkali metal	r_{c^+}[c)] (Å)	Solvent	Reaction time (h)	Total yield (mol%)	Products (mol%)		
						C-isomer	C,C-isomer	O-isomer
$CH_3OS(O)OCH_3$	Li^+	0.60	DMSO	52	38	63	2	35
$CH_3OS(O)OCH_3$	Li^+		DMSO	120	46	66	2	32
$CH_3OS(O)OCH_3$	Na^+	0.96	DMSO	39	52	47	1	52
$CH_3OS(O)OCH_3$	K^+	1.33	DMSO	40	39	41	1	58
CH_3I	Na^+		DMSO	22	quant.	81	16	3
$CH_3OS(O_2)OCH_3$	Na^+		DMSO	22	77	55	7	38
CH_3OTs[b)]	K^+		HMPA		96	7	4	89
CH_3Br[b)]	K^+		HMPA		87	42	44	14
CH_3I[b)]	K^+		HMPA		93	31	64	5

a) [Enolate]=0.5 mol/l. b) Data cited from Ref. 6, [enolate]=0.25 mol/l at 20 °C. c) Alkali metal cation radius.

depending on the size of the counter cation radius ($r_c{}^+$).

Leaving Group Effects. Results are listed in Table 2 together with the results reported for other methylating agents. Although it is difficult to compare rigorously among the data which have been obtained under the different reaction conditions,[6)] the O/(C+C,C)-alkylation ratio increases roughly in the order $I^- < Br^- < CH_3OS(O_2)O^- < CH_3OS(O)O^- < TsO^-$ (as listed in Table 2 data of Br^- and TsO^- cited from Ref. 6 and these have been obtained in HMPA with potassium salts). Methyl iodide in DMSO yields the C,C-isomer in higher yield compared with dimethyl sulfite.

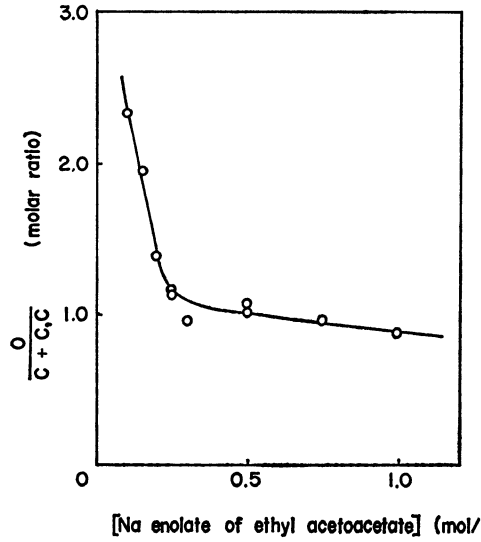

Fig. 1. Dilution effects on the O/(C+C,C)-alkylation ratio obtained with the sodium enolate of ethyl acetoacetate in DMSO at 50 °C.

Dilution Effects. As depicted in Fig. 1 the O/(C+C,C)-alkylation ratio tends to increase with increasing dilution, especially in a region of low enolate concentrations less than 0.3 mol/l pronounced dilution effects in DMSO was clearly appreciable.

Discussion

As shown in the preceding section the O/(C+C,C)-alkylation ratio of the alkali metal enolates of ethyl acetoacetate is affected by the size of the counter cation, solvent, leaving group, and dilution. The alkylation scheme is represented in Fig. 2 and according to this scheme an enhanced O/(C+C,C)-alkylation ratio of ambident anions is expected from the free ions. Kurts *et al.* measured the conductances of solutions containing alkali metal enolates and explained the enhanced ratios by the increased fraction of free ions.[4–6)] Dilution effects observed in a region of the low enolate concentrations less than about 0.3 mol/l also reflect the formation of the free ions (see Fig. 1).

On the other hand, solvent effects (Table 1) and counter cation effects in DMSO (Fig. 3) observed in the higher enolate concentration region more than 0.3 mol/l can be explained by the relative amounts of the two species, the contact and solvent-separated ion pairs, which were found to depend on the counter cation and the nature of the solvent. The solvent-separated ion pairs play an important role in the O/(C+C,C)-alkylation ratio when the fraction of the dissociated species, the free ions, is small, which is the similar situation to that proposed by Winstein *et al.* to account for the observed salt effects in the solvolysis of certain arene sulfonates.[10)]

The observed order of the solvent effects may be correlated to the solvating power to alkali metal ca-

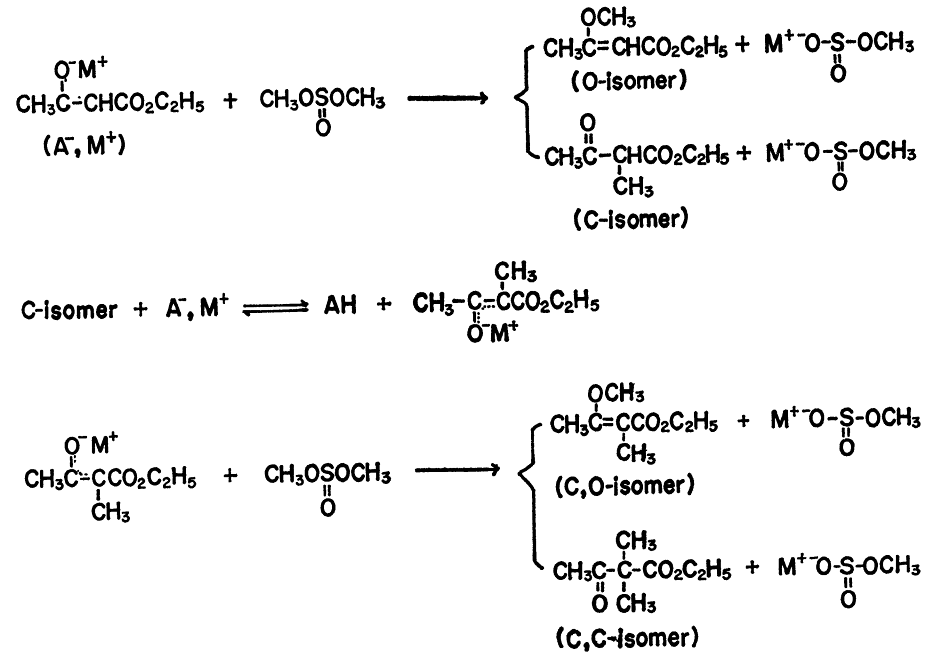

Fig. 2. Reaction scheme.

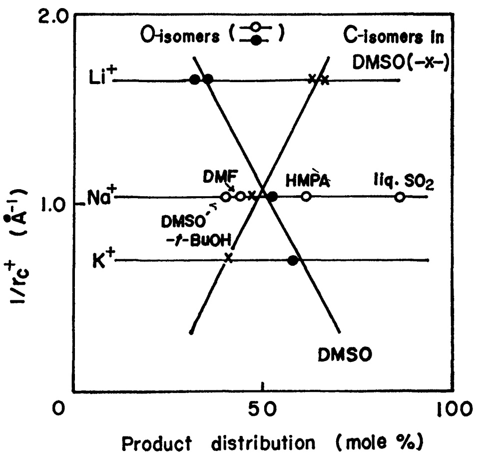

Fig. 3. Relationship between the inverse of the alkali metal cation radius ($1/r_c^+$) and the product distribution at 50 °C. ●, O-isomers in DMSO. ○, O-isomers in other solvents. ×, C-isomers in DMSO. Concentration of enolate was being kept constant at 0.5 mol/l.

tions. The solvating power does not depend on their dielectric constants, but on their ability to donate the negative charge to the cations.[11] The donor property is measured, for example, by solvent's "donicity"[12] and our O/(C+C,C)-alkylation ratio would be correlated with the donicity numbers rather than dielectric constants (see Table 1). DMSO and DMF are polarizable powerful bases like HMPA and the negative charge in their solvents is localized on a bare oxygen atom (nucleophilicity is centered on this oxygen[13]). The external solvation of HMPA, DMSO, or DMF to alkali metal cation tends to disperse the cationic charge and may contribute to weakening the coulombic interaction between the oxygen atom of the ambident anions and alkali metal cations. Thus in the DMSO, DMF, and HMPA, most of the fluorenyl salts (carbanions)[14] and thiolate salts (sulfur anions)[15] form solvent-separated ion pairs, even at room temperature. The polyethyleneglycol dimethyl ethers with the general formula, $CH_3O(CH_2CH_2O)_nCH_3$, referred to as glymes are effective alkali metal-solvating reagents[11] and have often been used to enhance the reactivity of organo-alkali metal compounds. Diglyme, $x=2$ in the general formula, can coordinate alkali metal cations using three coordinate sites. Our observed O/(C+C,C)-alkylation ratio in digylme is small than those in DMF, DMSO, and HMPA. Similar has been reported by Kornblum *et al.* that the O/C-alkylation ratio of sodium β-naphthoxide with benzyl bromide increased in the order tetrahydrofuran$\simeq$diglyme<DMF<DMSO[16] which is in accord with order observed in this study. Zook and Miller also found that the O/C-alkylation ratios of sodium enolate in DMSO are substantially larger than in diglyme and rates of enolate alkylation in DMSO are 10^3-fold greater than in glyme solvents.[17] These results may probably be due to the use of the sodium counter cation, and reactivity of diglyme is the most extensive for lithium salts.[18] The addition of *t*-butyl alcohol to DMSO lowered the O/(C+C,C)-alkylation ratio, since the protic solvent prevents the alkylating agent from approaching the oxygen atom of the ambident anion due to the formation of hydrogen bonding.

The size of the alkali metal cations strongly affects the fraction of tight ion pairs formed under otherwise identical conditions. Zaugg and Schaefer[18] found for the anions of phenols and enols that the fraction of the tight ion pairs decreases with increasing cation radius and that the absence of appreciable covalency interactions with alkali metals. The relationship between the inverse of the alkali metal cation radius ($1/r_c^+$) and the product distribution is depicted in Fig. 3. The larger the cation yields the higher the O-isomer; the fraction of O-isomer is proportional to the cation radius in DMSO. The oxygen atom of the alkali metal enolates of ethyl acetoacetate would be associated neither with solvent used nor with cations in these media except for liquid SO_2 (Reaction in liquid SO_2 is discussed below).

The structure of alkylating agents has also influence upon the alkylation. Although the results listed in Table 2 have been obtained under the different reaction conditions, the formation of enol ethers by methylating agents obviously depends on the nature of the leaving groups. In accordance with the hard soft acid base principle[20] the leaving group effects have been explained in terms of the symbiotic stabilization of the transition state; the more essential stabilization must be expected when both the leaving group and nucleophile are soft (or hard) Lewis bases.[21] Our results obtained by dimethyl sulfite, relatively high O/(C+C,C)-alkylation ratio, may be ascribed to that methyl sulfite anion as leaving group displays a fairly hard base, since the oxygen atom of enolate anions is a hard center.

The methylation in liquid SO_2 proceeds in a heterogeneous system which is rather assist to obtain the C-isomers. The observed O/(C+C,C)-alkylation ratio in liquid SO_2 is rather strangeness on the basis of the results obtained in aprotic and electron donating solvents, HMPA, DMSO, and DMF. Liquid SO_2 is also dipolar aprotic solvent, but behaves as an electron acceptor toward most of olefins and a large number of organic compounds having lone pair electrons.[22] Solvation of liquid SO_2 to alkali metal cations is not conceivable. Effects of liquid SO_2 is probably due to the stabilization for leaving groups, *i.e.*, methyl sulfite anion may be stabilized by the presence of electron accepting liquid SO_2.

Experimental

Solvents, HMPA, DMSO, DMF, diglyme, and liquid SO_2, were purified by usual methods. The alkali metal enolates of ethyl acetoacetate were prepared by addition of ethyl acetoacetate to the corresponding ethoxide salts, followed by the careful removal of ethanol and the dissolution of the remaining solid in solvent. Dimethyl sulfite was enclosed in the glass ampoule which was broken in a closed reaction vessel containing the alkali metal enolate of ethyl acetoacetate solution. Quantitative analysis of the four products was carried out by means of VPC.

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