

REACTIVITY OF AMBIDENT ANIONS—I KINETICS OF ALKYLATION OF ETHYL ACETOACETATE ALKALINE ENOLATES BY ETHYL TOSYLATE IN HEXAMETHYLPHOSPHOTRIAMIDE

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Abstract—Kinetics of alkylation of Li-, Na-, K- and Cs-enolates of ethyl acetoacetate by ethyltosylate in hexamethylphosphotriamide (HMPT) is reported.

In the range of concentrations 0.1–0.01 M the enolate ion was found to be the reacting species. The degree of dissociation of enolates in HMPT was measured by a conductometric method and the rate constants of O- and C-ethylations of the enolate ion were found from Acree's equation.

A comparison of the rate constants for O- and C-alkylations of sodium ethyl α -ethylacetoacetate by ethyl tosylate and ethyl iodide in DMF shows that the rates of ethyl iodide are higher for both centers. Thus the ambident anion studied is a relatively soft base.

FROM 1965 to 1969 a number of papers have appeared^{1–4} concerning the influence of factors that determine the ratio of O- and C-isomers in alkylation reactions of β -ketoester alkaline enolates in dipolar aprotic solvents. Attempts were made to find the conditions which would provide a maximum yield of the O-isomer. The mechanism of alkylation reactions of β -dicarbonyl compounds has been studied by Rhoads *et al.*^{5,6} where they reported the kinetics of alkylation of 2-carboethoxycyclohexanone sodium enolates by MeI and iso-PrI in DMSO and that of sodium ethyl α -ethylacetoacetate by iso-PrI in HMPT.

Continuing the investigation of enolate reactivity of β -dicarbonyl compounds^{7–11} we studied the kinetics of alkylation of Li-, Na-, K- and Cs-enolates of ethyl acetoacetate by ethyltosylate in the highly basic aprotic solvent HMPT.

The reason for using ethyltosylate as an alkylating agent is that it gives mainly monoalkylated products (dialkylation products were about 2%).

The ethylation reaction of ethyl acetoacetate alkaline enolates is second order, the rate being proportional to the concentration of each reagent. Provided the potassium

TABLE I. ETHYLATION OF POTASSIUM ENOLATE OF ETHYL ACETOACETATE BY ETHYLTOSYLATE IN HMPT AT 20.0°C, (a = enolate concentration; b = tosylate concentration)

a . 10 ² (mole/l)	b . 10 ² (mole/l)	k ₂ . 10 ³ (1/mole sec)
12.02	6.01	3.1
12.00	12.00	3.0
4.06	2.03	6.0
4.04	8.08	5.9
4.08	4.08	6.1

enolate concentration remains constant the rate constant does not depend on the ethyltosylate initial concentration. (Table 1).

However, with change of initial enolate concentration, the ethyltosylate concentration being constant, the reaction rate constants vary over a very large range. An increase in constant was observed when the initial enolate concentration decreased (Table 2, Fig 1).

TABLE 2. ETHYLATION OF ETHYL ACETOACETATE ALKALINE ENOLATES BY ETHYLTOsylATE IN HMPT, $C_{\text{enolate}} = C_{\text{EtOTs}}$, $t = 20.0^\circ\text{C}$

Metal	$c \cdot 10^2$ (mole/l)	$k_2 \cdot 10^3$ * (1/mole sec)	k_2/k_0
Li	2.00	0.34	0.13
	4.00	0.23	0.13
	6.00	0.14	0.13
	8.00	0.12	0.13
Na	2.00	5.7	0.13
	4.00	4.0	0.13
	6.00	3.5	0.13
	8.30	3.0	0.13
K	1.06	9.4	0.13
	2.06	7.7	0.13
	4.08	6.1	0.13
	5.53	5.0	0.13
	7.28	4.2	0.13
	10.28	3.2	0.13
Cs	1.00	12.5	0.13
	1.92	10.8	0.13
	4.01	8.7	0.13
	8.00	6.0	0.13

* Constants are an average of three (or more) independent runs. The deviation is $\pm 5\%$.

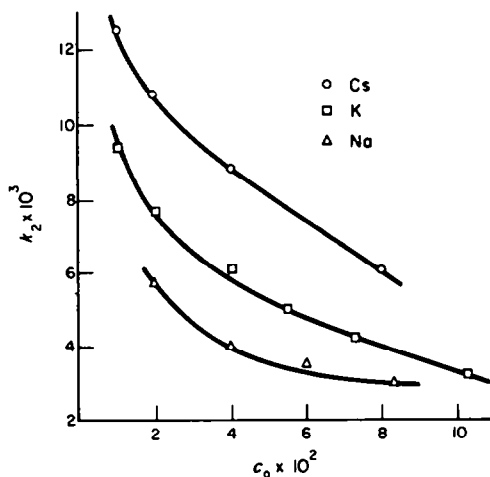
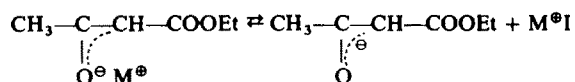


FIG 1. Dependence of ethylation rate constants on the initial concentration of alkaline enolate of ethyl acetoacetate.

Such a change in rate constant is produced by the different degree of enolate dissociation within the working range of concentrations.

It should be noted that some decrease in rate constant was observed during kinetic plot. Thus the values of the rate constants were determined in all cases by extrapolation of the observed values to zero time.

Taking into account the increase in the rate constant with dilution of reaction mixture, one would expect the opposite effect. The decrease in rate constant in the course of the reaction is apparently due to the common cation effect (the alkali metal cation is formed from alkaline toluenesulfonate, that is produced in the reaction). The equilibrium (I) is then shifted to the left, favouring the formation of non-dissociated species.



This effect is apparently the more important and overcomes the dilution effect. This view is supported by the fact that the addition of even an equimolar amount of sodium toluenesulfonate to the sodium ethyl acetoacetate reaction mixture ($C = 4.24 \times 10^{-2}$) causes a decrease of the reaction rate of 1.5 with respect to the rate constant without salt added. Addition of a ten-fold quantity of sodium perchlorate causes a 15-fold decrease of k_2 .*

A similar phenomenon has been observed by Ugelstadt *et al.* in the study of alkylation kinetics of sodium and potassium phenolates in dimethylformamide and tetraglyme.¹² The decrease in rate constant over kinetic plot due to salt formation has also been stated in the methylation of sodium phenolate by MeI in MeCN and benzonitrile.¹³

In the ethylation of ethyl acetoacetate enolates there was also a decrease of k_c/k_0 from 0.13 at the beginning of the reaction to 0.10 at the end. This can be explained by the formation of a small quantity (~2%) of the dialkylation product. This is confirmed by the constancy of the rate constant ratio for the carbon and oxygen centers (k_c/k_0) in the course of the ethylation reaction of sodium ethyl α -ethylacetoacetate (Table 3). For all enolates the ratio k_c/k_0 was 0.13 at the beginning of the

TABLE 3. ETHYLATION OF SODIUM ETHYL α -ETHYL-ACETOACETATE BY ETHYLTOsylATE IN HMPT, $t = 25^\circ\text{C}$. $C_{\text{enolate}} = C_{\text{tosylate}} = 5.03 \times 10^{-2}$ mole/l

conversion %	k_c/k_0
10	0.91
30	0.90
50	0.91
60	0.90
70	0.90
80	0.90
100	0.90

* In this case a 1.4-fold increase in the C-isomer portion was also observed.

reaction. This allows us to assume that within the range of concentrations studied the only reacting particle is the enolate ion.

To determine the true ethylation rate constant of the ethyl acetoacetate anion the dissociation of sodium, potassium and caesium enolates in HMPT was studied

TABLE 4. DEGREES OF DISSOCIATION OF ETHYL ACETOACETATE ALKALINE ENOLATES IN HMPT AT 20.0°C

Metal	$c \cdot 10^2$ mole/l	α
Na	8.30	0.18
	6.00	0.21
	4.00	0.25
	2.00	0.33
K	7.28	0.27
	5.53	0.29
	4.08	0.33
	2.06	0.45
Cs	1.06	0.55
	8.00	0.36
	4.01	0.48
	1.92	0.60
	1.00	0.70

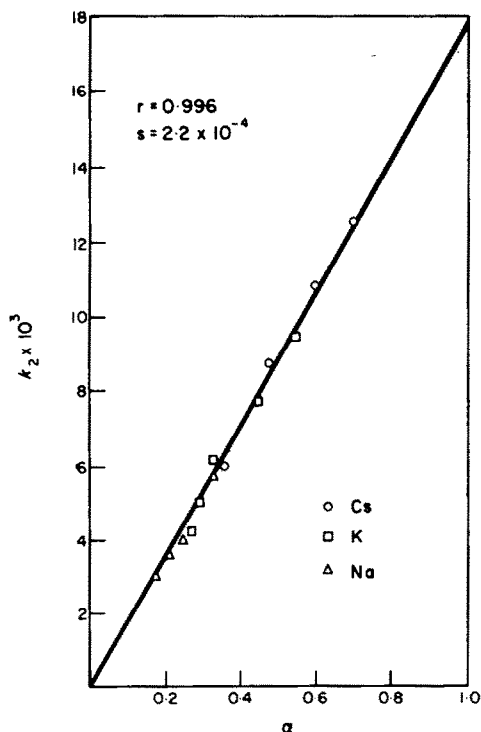


FIG. 2. Plot of k_2 vs. α for ethylation of alkaline enolates of ethyl acetoacetate by ethyltosylate in HMPT

conductometrically. From the data given in Table 4 it follows that the degree of dissociation, α , increases from sodium to caesium enolate.

From the equation $k_2 = k_i\alpha + k_m(1 - \alpha)^{14}$ the true rate constants k_i and k_m of the ion and ion pair respectively can be obtained.

The plot of k_2 vs α (Fig 2) shows that for all enolates the rate constant values fall on a straight line passing through the coordinate center. Therefore under the conditions described the only reacting particle is the enolate ion and $k_2 = \alpha k_i$, ($k_i = 1.8 \times 10^{-2}$ 1/mole sec). For each center the rate constants are $k_{01} = 1.6 \times 10^{-2}$ and $k_{c1} = 2 \times 10^{-3}$ 1/mole sec ($k_c/k_0 = 0.13$).

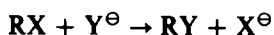
It is interesting to compare the kinetic data of alkylation of β -ketoester alkaline enolates in polar aprotic and protic solvents. The alkylation of Li-, Na-, K-, Rb- and Cs-enolates of ethyl acetoacetate by MeI in EtOH has been studied by Brändström.¹⁵ Under these conditions only C-alkylation products are formed, both the ion and the ion pair participate in the reaction and ordinary reactivity is observed: the ion reacts faster than the ion pair. It is important to note that although the degrees of dissociation of Na-, K- and Cs-enolates of ethyl acetoacetate in EtOH and in HMPT are rather close, in the aprotic medium the only reacting particle is the enolate ion.

Forsblad has determined the values of k_i and k_m for the methylation of Li-, Na-, and BP*-enolates of β -hydroxycoumarilic ester by MeI in MeOH.¹⁶ In the case of the ionic mechanism the rate constant of both the C- and O-alkylation reactions did not depend on the metal but the reaction rate constant of the ion pair increased with increase of the cation radius.

Thus in the case of the O-methylation reaction $k_i > k_m$ only for the Li-enolate, whereas for Na-, K- and BP-enolates $k_m > k_i$ (for the BP-enolate $k_m/k_i = 3.6$). In C-methylation $k_i > k_m$ for all enolates except BP. For the latter $k_m/k_i = 2.4$. Thus for the BP-enolate in both C- and O-alkylations the reaction rate constant of the ion pair exceeds that of the ion. In our opinion it can be explained by a "hard-hard" type solvation of the oxygen center of the anion with protic solvent.

Therefore shielding of the oxygen center of the anion with a hydrogen bond appears to be more essential than the electrostatic attraction of BP-cation in the ion pair.

Recently the ratio k_{Br}/k_{OTs} has been proposed as a measure of softness (hardness) of the nucleophilic agent Y^\ominus in S_N2 reactions.¹⁸



A large value for this ratio indicates the symbiotic stabilization of the transition state,¹⁷ when the nucleophilic agent is a soft base. A small value indicates the same phenomenon in the case of a hard Y^\ominus .

Thus the ratio of the rate constants for the reaction of the given anion with alkyl iodide (bromide) and alkyltosylate is a quantitative measure of the nucleophilic agents polarizability. For ambident nucleophilic agents the ratio k_i/k_{OTs} characterizes a different degree of hardness for both centers of mesomeric anion.

We have studied the kinetics of alkylation of sodium ethyl α -ethylacetoacetate by EtBr, EtI and EtOTs in dimethylformamide (Table 5). The effective rate constants

* BP—bispiperidinium cation

are presented in Table 5. From these data it follows that for C-alkylation $k_f/k_{OTs} = 420$, whereas for O-alkylation $k_f/k_{OTs} = 13$.

Thus for rather soft ambident anions a higher transition state stability can be also attained when the leaving group is a soft base, even if their hard center participates in the reaction.

TABLE 5. ALKYLATION OF SODIUM ETHYL α -ETHYLACETOACETATE IN DMF AT 20° C.

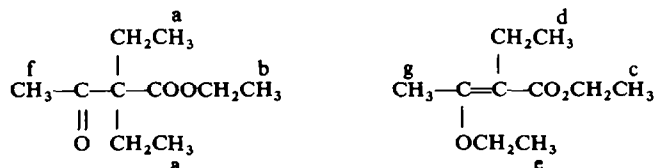
$$C_{\text{enolate}} = C_{\text{EtX}} = 4.20 \times 10^{-2} \text{ mole/l}$$

X	k_2	k_c/k_0	k_0	k_c
OTs	9.10×10^{-4}	1.87	3.17×10^{-4}	5.93×10^{-4}
Br	1.40×10^{-2}	27	5×10^{-4}	1.35×10^{-2}
I	0.25	64	$\sim 4 \times 10^{-3}$	0.25

EXPERIMENTAL

Hexamethyltriimidophosphate, commercial "Schuchardt" reagent was purified by heating *in vacuo* (1 mm Hg) at 80° (15 hr) distilled in argon over CaH₂. The dimethylamine free fraction was collected. HMPT was distilled twice, b.p. 95–96°/3 mm, n_D^{21} 1.4574, lit. n_D^{20} 1.458,¹⁹ $\kappa = 4 \cdot 10^{-8}$ – $5 \cdot 10^{-8}$ ohm⁻¹cm⁻¹. Dimethylformamide was purified by the method given by Parker.²⁰ Alkaline enolates of ethyl acetoacetate were prepared from the corresponding tert-butylates of alkaline metal and ethyl acetoacetate in absolute ether using the procedure described for potassium ethyl acetoacetate.⁷ The purity was no less than 97%. For quantitative GLC analyses the following compounds were used as standards. Ethyl α -ethylacetoacetate and Ethyl β -ethoxycrotonate were prepared by the earlier described procedure.⁷

Ethyl α, α -diethylacetoacetate and ethyl α -ethyl- β -ethoxycrotonate. A solution of 2.30 g (0.011 mole) of ethyltosylate in HMPT (15 ml) was added dropwise at stirring to 2.06 g (0.11 mole) of 2-sodium ethyl α -ethylacetoacetate in HMPT (15 ml). After the reaction was completed the mixture was poured into water and ether extracted, dried over MgSO₄, solvent evaporated and residue distilled *in vacuo*, b.p. 47–48°/3 mm, 1.61 g (75%). (Found: C, 64.67; H, 9.60. C₁₀H₁₈O₃ requires: C, 64.51; H, 9.60%). GLC showed a mixture of two substances (1 : 1) one being ethyl α, α -diethylacetoacetate. The second corresponding



to ethyl α -ethyl- β -ethoxycrotonate (IR and NMR). NMR spectrum (δ): (a) 0.78 (6 H, t); (b) 0.95 (3 H, t); (c) 1.32 (3 H, t); (d) 1.35 (3 H, t); (e) 1.84 (3 H, t); (f) 2.11 (3 H, s); (g) 2.40 (3 H, s), multiplet from the methylene protons signals in the region of 3.85–4.4 ppm. IR spectrum: C=C 1628, C=O 1742, 1718 cm⁻¹.

Kinetic measurements. The reaction kinetics was measured by backward titration. The reaction was conducted with stirring in a thermostated cell under argon. The k_c/k_0 ratio was determined by GLC. Chromatographic analysis was carried out on gas-liquid Chrom-2 Chromatograph using flame ionization detector (column 2 m, diameter 4 mm with 17% apiezon-L on chromosorb W), gas nitrogen, column temp. 110°, N₂ rate 100 ml/min.

Conductance measurements. The conductivity studies were carried out using an apparatus consisting of an alternating current bridge MPT-5 with a set of resistance from 0.1 to $1 \cdot 10^6$ ohm (sensitivity $\pm 1\%$).

A 5 ml cell with a cylindrical Pt electrode and a constant $k = 8 \cdot 0 \times 10^{-3} \text{ cm}^{-1}$ was used. Starting concentrations of enolates solutions were 8×10^{-2} mole/l. Other solutions were obtained by subsequent dilution. The conductometric cell was flushed before every measurement with dry argon (10 min), then filled with the solution and thermostated at 20.0°C for 15 min.

Conductivity data for sodium ethyl acetoacetate in HMPT at 20.0°C.

$C \times 10^4$ (mole/l)	R (ohm)	($\text{cm}^2 \text{equiv.}^{-1} \text{ohm}^{-1}$)	α
830	47	2.05	0.180
625	55	2.32	0.208
415	70	2.75	0.241
207.5	101	3.82	0.327
103.7	156	4.94	0.407
51.9	240	6.40	0.516
26.9	383	8.03	
13.0	640	9.60	
6.50	1130	10.8	
3.25	2120	11.5	

$$\lambda_0 = 14.0 \text{ cm}^2 \text{equiv.}^{-1} \text{ohm}^{-1}$$

Conductivity data for caesium ethyl acetoacetate in HMPT at 20°C.

$C \times 10^4$ (mole/l)	R (ohm)	($\text{cm}^{-2} \text{equiv.}^{-1} \text{ohm}^{-1}$) α	
800	28	3.58	0.356
400	40	5.00	0.479
200	62	6.45	0.594
100	101	7.92	0.695
50	173	9.25	0.789
25	302	10.6	
12.5	568	11.9	
6.25	1100	11.5	

$$\lambda_0 = 13.6 \text{ cm}^2 \text{equiv.}^{-1} \text{ohm}^{-1}$$

The equivalence conductance, λ , at each concentration was calculated in the usual way and an initial estimate of the limiting conductance λ_0^1 was made by extrapolation of a λ vs. \sqrt{C} plot. From the values of λ and λ_0^1 an approximate value of α was calculated and a new plot λ vs. $\sqrt{\alpha C}$ was made to obtain a better value of λ_0 .

Conductivity data for potassium ethyl acetoacetate in HMPT at 20.0°C.

$C \times 10^4$ (mole/l)	R (ohm)	λ ($\text{cm}^2 \text{equiv.}^{-1} \text{ohm}^{-1}$)	α
823	41	2.37	0.273
600	48	2.79	0.279
411.5	57	3.40	0.334
328	63	3.87	0.369
205.75	82	4.75	0.451
102.9	127	6.12	0.559
51.4	205	7.59	0.672
25.7	346	8.99	
12.66	616	10.19	
6.43	1170	10.6	

$$\lambda_0 = 13.0 \text{ cm}^2 \text{equiv.}^{-1} \text{ohm}^{-1}$$

D—dielectric constant of HMPT equal to 30²² η —viscosity of HMPT equal to 0.0344 poise^{6, 23}

T—absolute temperature equal to 293°K.

The process was repeated until the λ_0 value obtained in successive cycles showed no change. The degree of dissociation was calculated from the equation*.²¹

$$\alpha = \frac{\lambda(1 + 2.303 S\sqrt{\alpha C})}{\lambda_0(1 + 2.303\sqrt{\alpha C} - S\sqrt{\alpha C/\lambda_0})}$$

where

$$S = \frac{1.825 \times 10^6}{(DT)^{\frac{1}{2}}} = 2.215$$

$$S_\lambda = \frac{8.2 \times 10^5}{(DT)^{\frac{1}{2}}} \lambda_0 + \frac{82.4}{\eta(DT)^{\frac{1}{2}}} = 0.995\lambda_0 + 25.58$$

* The determination of α by Shedlovsky's method was unsuccessful because in the concentration region studied the plot $1/\lambda S(z)$ vs $\lambda S(z)$ cf^2 was non-linear. Therefore α was calculated by Grunwald's method, which permits the determination in a region of rather high concentrations.¹⁵ This method was also used by Rhoads and Holder⁶ in the calculation of the degree of dissociation of sodium ethyl α -ethylacetoacetate in HMPT.

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