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A COMPARATIVE STUDY OF C- AND O-ALKYLATION IN CYCLIC AND ACYCLIC β-KETO ESTER SYSTEMS*†

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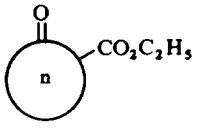
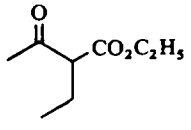
Abstract—Isopropylation of the sodium salt of ethyl α-ethyl-acetoacetate, II, has been studied kinetically in two aprotic solvents, DMSO and HMPT. Second order rate constants for C-alkylation, O-alkylation, and propene formation are compared with those of the cyclic β-keto ester systems, I-n. In each reaction mode, the acyclic enolate is significantly more reactive than the cyclic ones. Conductance studies suggest that the greater reactivity of the sodium enolate of II may be attributed to its higher degree of dissociation in the aprotic solvents and the ability of the free ion to assume a "W" shape. The superior ability of HMPT to enhance nucleophilic reactivity, in general, and to promote O-alkylation, in particular, is noted.

IN EXTENSION of earlier work on competitive C- and O-alkylation of the cyclic β-keto esters, I-n,[1a] § the isopropylation of an acyclic analog, ethyl α-ethylacetoacetate, II, has been examined kinetically in two aprotic solvents, DMSO and HMPT. In both solvents, reaction of the sodium enolate of II (E) with isopropyl iodide proceeds by

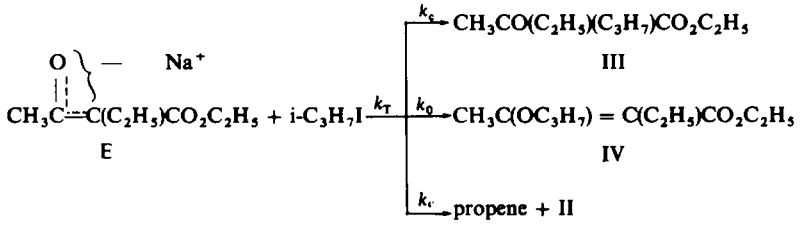


I-n : n = 5, 6, 8



II

three concurrent second order processes to yield the C-alkylated derivative, III, the O-alkylated derivative, IV, and the products of a bimolecular elimination, propene and an equivalent amount of II. The total reaction was followed titrimetrically and the



$-d(E)/dt = k_T(E)(i\text{-}C_3H_7I)$ where $k_T = k_c + k_0 + k_e$

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§ S. J. Rhoads and R. W. Hasbrouck, *Tetrahedron*, 22, 3557 (1966). The background for this problem and leading references for the general problem of alkylation of ambident anions are given in this paper. More recent reports on C- and O-alkylation of β-keto esters in aprotic solvents included in Refs 1*b* and 1*c*.

individual rate constants, k_e, k_0, and k_e were evaluated by the method described earlier[1a] with the modification that the appearance of II in the reaction products was used as a measure of the elimination process. The alkylation products, III and IV, were isolated by preparative GLPC and their structures established by spectral analysis (Experimental). The rate data for the alkylation of II in the two solvents are summarized in Table I. Table 2 lists the corresponding activation quantities.

TABLE 1. SUMMARY OF RATE CONSTANTS FOR THE ISOPROPYLATION OF ETHYL *sodio*-α-ETHYLACETOACETATE IN DMSO AND HMPT

Solvent	Temperature °C	$k_T^a \times 10^3$ 1/mole-sec	$k_c^a \times 10^3$ 1/mole-sec	$k_0^a \times 10^3$ 1/mole-sec	$k_e^a \times 10^3$ 1/mole-sec	C/O
DMSO	20·00 ± 0·03	10·30 ± 0·13	9·14 ± 0·35	0·78 ± 0·07	0·37 ± 0·15	11·7
	25·00 ± 0·03	15·34 ± 0·16	13·31 ± 0·41	1·30 ± 0·08	0·75 ± 0·30	10·2
	30·00 ± 0·03	20·75 ± 0·40	17·02 ± 0·68	1·96 ± 0·26	1·58 ± 0·58	8·69
	35·00 ± 0·03	33·63 ± 0·08	26·69 ± 0·42	3·42 ± 0·07	3·53 ± 0·27	7·80
	40·15 ± 0·03	47·68 ± 0·16	38·10 ± 0·08	4·89 ± 0·01	4·70 ± 0·10	7·80
HMPT	20·00 ± 0·03	74·91 ± 3·70	54·97 ± 2·94	17·17 ± 0·55	2·80 ± 0·24	3·20
	25·00 ± 0·03	113·6 ± 0·2	83·28 ± 1·55	25·49 ± 0·16	4·85 ± 1·56	3·26
	30·00 ± 0·03	164·8 ± 1·8	118·4 ± 1·0	37·49 ± 0·41	8·81 ± 1·13	3·16

[a] Uncertainties are average deviations of at least two independent runs.

TABLE 2. ACTIVATION QUANTITIES FOR THE ISOPROPYLATION OF ETHYL α-ETHYLACETOACETATE IN TWO SOLVENTS AT 30°

Solvent	Alkylation mode	$\Delta H^{\ddagger a}$ kcal/mole	$\Delta S^{\ddagger a}$ e.u.
DMSO	C	12·4 ± 0·8	−25·7 ± 2·5
	O	16·3 ± 0·8	−17·0 ± 2·5
HMPT	C	12·0 ± 1·5	−23·3 ± 5·0
	O	13·5 ± 1·5	−20·6 ± 5·0

[a] Uncertainties are statistical errors assessed from an estimated ± 6% precision in the individual rate constants based on the maximum errors arising from the combination of errors in k_T, k_e, and the C/O ratios. See Ref. 1*a*.

The effectiveness of aprotic solvents in promoting the O-alkylation mode is demonstrated by the data in the last column of Table 1. The C/O ratios recorded there may be contrasted with a C/O ratio of ~24 for the same reaction in the protic solvent, ethanol.[2] Also evident is the superior power of HMPT over that of DMSO, both in its general enhancement of nucleophilic reactivity and its special enhancement of the O-alkylation process.[1c, 3, *] It is noteworthy that the latter effect reflects mainly in the enthalpy of activation (Table 2).

[*] Although rate data for the cyclic β-keto esters in the "super" solvent, HMPT, are not available, preparative alkylations show that the enhancement of the O-alkylation mode prevails with those, also. Thus, the following C/O ratios are found for iso-propylation in HMPT for solutions *ca.* 0·1M in enolate: I-5, 0·7; I-6, 0·3; I-7, 1·3; I-8, 3·6; I-10, 10·9.

To facilitate comparison of the acyclic and cyclic systems, rate data for II at 30° in DMSO along with those obtained earlier for I-n[1a] are set forth in Table 3. The most striking difference is that of the total rate of reaction (k_T) in the open chain system in comparison with those in the cyclic systems. Compound II is more reactive

TABLE 3. RATE DATA FOR THE ISOPROPYLATION OF β-KETO ESTERS IN DMSO AT 30°

Compound	$k_T^a \times 10^4$ 1/mole-sec	$k_c^a \times 10^4$ 1/mole-sec	$k_0^a \times 10^4$ 1/mole-sec	$k_e^a \times 10^4$ 1/mole-sec
I-5[b]	17·1 ± 0·6	9·15 ± 0·62	5·25 ± 0·35	2·70 ± 0·24
I-6[b]	12·0 ± 0·1	5·33 ± 0·23	3·97 ± 0·16	2·70 ± 0·19
I-8[b]	33·0 ± 0·7	23·3 ± 1·2	3·01 ± 0·16	6·80 ± 0·51
II	207·5 ± 4·0	170·2 ± 6·8	19·6 ± 2·6	15·8 ± 5·8

[a] Uncertainties are average deviations of at least four independent runs.
[b] Data from Ref. 1a.

than the most reactive of the cyclic keto esters, I-8, by a factor of six—a surprising result in view of the comparable basicities and nucleophilicities of their anions in the solvent ethanol.[4] Moreover, II exhibits this greater reactivity in each component of the total reaction, k_c, k_0, and k_e. This unexpected behavior of II within the reaction series is revealed in another way by consideration of the relative rates of the C-alkylation mode, alone, in the two reaction systems, i-C_3H_7I/DMSO and CH_3I/C_2H_5OH.[4] The ratios shown in Table 4 reflect the balance of effects on the

TABLE 4. RELATIVE RATES OF C-ALKYLATION OF β-KETO ESTERS IN TWO REACTION SYSTEMS AT 30°

Compound	I-5	I-6	I-8	II
$\frac{k_c\ C_3H_7I/DMSO}{k_c\ CH_3I/C_2H_5OH^a}$	0·33	0·29	0·26	1·8

[a] Data from Ref. 4.

rates of C-alkylation when the alkylating medium is changed from an alkylating agent of low reactivity in a rate enhancing solvent (i-C_3H_7I in DMSO) to one of a highly reactive alkylating agent in a less effective solvent (MeI in EtOH). For the cyclic systems, the net effect is that the rate of C-alkylation in the first system is *diminished* by a factor of three to four from that observed in the methyl iodide-ethanol system. The acyclic β-keto ester, however, is *more* reactive in the aprotic solvent than in the protic one, by a factor of 1·8, despite the opposing change in alkyl iodide reactivity. The striking difference in the reactivity of the acyclic and cyclic systems illustrated by these comparisons suggests that in the aprotic solvents the acyclic anion can achieve a condition of high reactivity that is not available to it in the protic solvent and which is not available to the cyclic anions in either type of solvent.

It is generally held that free ions are more reactive than the corresponding ion pairs and higher ionic aggregates[5] and this explanation may reasonably be invoked

to account, at least in part, for the enhanced reactivity observed for anionic nucleophiles in aprotic, dipolar solvents.[6] To test the possibility that the contrasting reactivities of the sodium salts of II and I-n in DMSO could be traced to a difference in the concentration of free enolate ions in these systems, conductance measurements were undertaken.

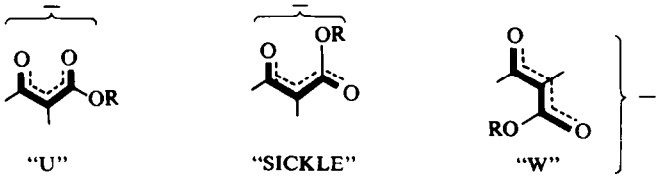
The conductivity behavior of II in DMSO and HMPT and of I-n in DMSO was studied at 25° and in concentrations ranging from 0·0002 to 0·05M. The conductance data, treated by the method outlined by Forsblad,[7] yielded the dissociation values summarized in Table 5 for ~ 0·05M solutions, which correspond to those used in the kinetic runs. Clearly, there is a marked difference in the extent of dissociation of the acyclic and cyclic salts at this concentration. The sodium enolate of II shows fairly extensive dissociation (~40–50%) whereas the degree of dissociation of the salts of the cyclic systems is minor (~3–5%). The major factor responsible for the contrasting reactivities of the acyclic *vs* cyclic systems in the aprotic solvent DMSO, does, indeed, appear to be the relative abundance of free enolate ions in the acyclic case.* There remains, however, the interesting question of why there should be such disparate degrees of dissociation of the salts of acyclic and cyclic systems in DMSO.

TABLE 5. DISSOCIATION OF SODIUM ENOLATES OF β-KETO ESTERS IN APROTIC SOLVENTS AT 25°

Sodium enolate	$C \times 10^2$ mole/l	Solvent	% Dissociation
II	4·738	DMSO	39·9
II	5·103	HMPT	48·3
I-5	5·000	DMSO	5·3
I-6	5·110	DMSO	3·8
I-8	5·028	DMSO	2·8

An answer to this question may be sought in the geometries available to the free enolate ions derived from cyclic and acyclic β-keto esters and the stabilities of these geometries in an aprotic solvent. In general, three major conformations come under consideration for planar enolates of β-dicarbonyl compounds, the "U" shape, the "sickle" shape, and the "W" shape.[8] The enolate ions derived from the keto esters, I-n, are constrained to a "U" or "sickle" shape by their cyclic structures, even in the free anion in which the stabilizing effect of the cation has been removed. In aprotic solvents, which only poorly solvate anions,[9] the dipole–dipole interaction of the ends of the enolate system would be expected to destabilize the free ions of I-n relative to the ion pairs, thus favoring association despite the high affinity of the solvent molecules for the cation. On the other hand, the free enolate ion of the acyclic structure can adopt the alternative "W" shape in which the dipole–dipole interaction is minimized. In this case, promotion of dissociation by cation solvation would be less strongly opposed.

* This conclusion is further substantiated by the observation that the value of k_T increases with dilution. A kinetic run in HMPT at 30° with $[E]_0 = [i\text{-PrI}]_0 = 0·0077$ M gave a value of k_T of 356×10^{-3} l/mol-sec, more than double the value obtained with initial reactant concentrations of 0·0387 M. The dilution effect is commonly observed for reactions of the type studied here and is attributed to the greater contribution of the free ion component to the total reaction. Ref. 5.

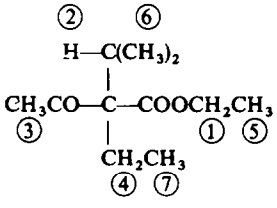
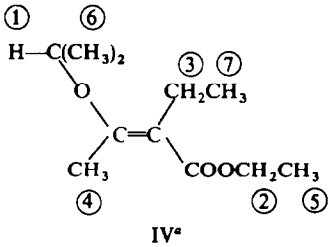


The situation in the protic solvent, ethanol, appears to be quite different. Zaugg and Schaefer[8] have presented spectral evidence that enolates of acyclic β-dicarbonyl compounds, which in principle can adopt either the "U" or "W" shape, remain in the "U" shape conformation and in some form of association, even in dilute, ethanolic solution. The *similar* reactivities of the enolates of II and I-8 observed in ethanol[4] appear to be in harmony with this picture.

EXPERIMENTAL

Reagents and general methods. Baker Analyzed Reagent DMSO, dried by the method described,[1a] showed a specific conductance of $4{\cdot}1 \times 10^{-7}$ ohm^{-1} cm^{-1} and was used in all kinetic and conductance work. Eastman Kodak reagent HMPT was dried over 4A Molecular Sieves before use. This material had a specific conductance of $5{\cdot}8 \times 10^{-6}$ ohm^{-1} cm^{-1} and a viscosity of 0·0330 poise. Isopropyl iodide for kinetic runs was purified and stored as described earlier.[1a] UV spectra were run in matched silica cells in a Beckman DB spectrophotometer. IR spectra were measured as thin films with a Beckman IR 10 instrument A Varian A-60 spectrophotometer was used to obtain the NMR spectra which were determined on solns in CCl_4 with TMS as an internal standard.

TABLE 6. SPECTRAL PROPERTIES OF ETHYL-2-ISOPROPYL-3-KETOBUTANOATE (III) AND ETHYL 2-ETHYL-3-ISOPROPOXY-2-BUTENOATE (IV)

Compound	UV	IR	NMR
	(λ_{max}^{EtOH}, ε)	(cm^{-1})	(proton, δ, multiplicity, area)
 III	285 mμ, 76	1740, 1725 str. 1710 str.	①4·16, q, 2 ②2·22, m, 1; ③2·06, s, 3; ④1·80, m, 2; ⑤1·28, t, 3; ⑥0·88, d, 6; ⑦0·73, t, 3.
 IV[a]	250 mμ, 8,900	1701 str. 1621 str.	①4.42, m, 1; ②4·09, q, 2; ③2·3, m, 2; ④2·25, br s, 3; ⑤1·26, t, 3; ⑥1·2, d, 6; ⑦0·92, t, 3.

[a] The geometry shown for IV with the oxygenated functions *trans* is supported by the chemical shift values for the alkyl substituents at the double bond by comparison with *cis* and *trans* isomers of known geometry. Unpublished experiments, this laboratory.

Preparative alkylation. The C- and O-isopropylated derivatives of II were isolated by preparative GLPC using a 2·6 m Perkin-Elmer "K" column at a temp of 162° from a preparative alkylation carried out in the manner previously detailed.[1a] The compounds were purified by recycling. The structures of the C-derivative, III, and the O-derivative, IV, follow from their spectral properties (Table 6) which correspond in all important details to those of C- and O-derivatives reported earlier.[1a]

Kinetic studies. The total rate constants, k_T, for the reactions of the enolate of II with isopropyl iodide in DMSO and HMPT were measured by the titrimetric procedure outlined earlier.[1a] The ratio of C-alkylation : O-alkylation : propene formation could be determined directly in this system by integration of GLPC traces (Perkin–Elmer K column, 2 m in length at 130°) of reaction mixtures for III, IV, and II at the end of kinetic runs (allowed to proceed for 10 half-lives).* This procedure for the evaluation of k_e. was checked by the independent determination of propene formation employed in the earlier work[1a] and the results were found to agree well within the experimental error of the original procedure. Sample data at 25° in the two solvents appear in Table 7.

TABLE 7. ISOPROPYLATION OF ETHYL-*sodio*-α-ETHYLACETOACETATE IN DMSO AND HMPT AT 25°

$(E)_0$ mole/l	$(i\text{-PrI})_0$ mole/l	$k_T \times 10^3$ 1/mole-sec	$k_c \times 10^3$ 1/mole-sec	$k_0 \times 10^3$ 1/mole-sec	$k_e \times 10^3$ 1/mole-sec
DMSO					
0·0496	0·0496	15·48	13·72	1·30	0·46
0·0496	0·0496	15·18	13·33	1·17	0·68
0·0496	0·0994	15·50	13·19	1·36	0·95
0·0496	0·0994	15·20	13·00	1·38	0·82
		Av. 15·34 ± 0·16	13·31 ± 0·41	1·30 ± 0·08	0·75 ± 0·30
HMPT					
0·0432	0·0432	113·5	84·83	25·33	3·29
0·0432	0·0432	113·8	81·74	25·65	6·41
		Av. 113·6 ± 0·2	83·29 ± 1·55	25·49 ± 0·16	4·85 ± 1·56

Conductance measurements. The conductivity studies were carried out using a Leeds and Northrup Wheatstone bridge apparatus consisting of a 1553 Ratio Box, a 1185 Air Capacitor, and a General Radio Type 1432-X Decade Resistance Box with ratio arms supplying seven multiplying values. A signal of 1900 c/s at one volt was supplied by a Heathkit AG-9A audio generator. The signal was tuned by a General Radio Tuned Amplifier which also served as the null detector for the measurements. Connected to an additional, optional resistor, the entire assembly was capable of measuring resistances from 0·1 to 1,999,999·9 ohms with a reproducibility of ± 0·5%. A Leeds and Northrup conductance cell (4914) of ca. 35 ml capacity with lightly platinized electrodes and cell constant of 1·2431 cm^{-1} was used in all measurements. Enough of the dry, powdered sodium salt of the β-keto ester was weighed out and diluted with dry, pure solvent to make a 0·05W stock solution. Other solutions were made by appropriate dilutions of this stock soln. After 15–30 minutes equilibration in a constant temp bath held at 25° the resistance of the soln was measured.

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 value of Λ and Λ_0^1, an approximate value of α, the fraction dissociated, was calculated and a new plot of Λ *vs* $\sqrt{\alpha C}$ was made to obtain a better value of Λ_0. The process was repeated until the Λ_0 value obtained in successive cycles showed no change. A best value for the fraction dissociated, α, was then calculated from the equation*

$$\alpha = \frac{\Lambda(1 + 2{\cdot}303\, S_V \alpha C)}{\Lambda_0(1 + 2{\cdot}303\, S_V \sqrt{\alpha C} - S_A \sqrt{\alpha C}/\Lambda_0)}$$

* Unlike the cyclic keto esters, II shows no tendency to decompose on GLPC columns but gives symmetrical peaks which can be integrated with good reproducibility and accuracy.

where S = limiting slope of Debye-Hückel equation
S_A = limiting slope of the Onsager equation.

Table 8 summarizes the conductance data and degrees of dissociation for five concentrations of the sodium enolate of II in DMSO and HMPT. Table 9 gives the corresponding data for the salts of the cyclic keto esters. II-n, in DMSO.

TABLE 8. CONDUCTIVITY DATA FOR ETHYL *sodio*-α-ETHYLACETOACETATE IN DMSO AND HMPT AT 25·0°

$C \times 10^4$ mole/l	R ohms	Λ $cm^2\ equiv^{-1}\ ohm^{-1}$	α
DMSO $\Lambda_0 = 37{\cdot}7\ cm^2\ equiv^{-1}\ ohm^{-1}$			
2·369	172,000	30·9	0·836
4·738	92,000	28·6	0·778
23·69	25,400	20·6	0·576
47·38	13,200	20·0	0·570
473·8	2.048	12·8	0·399
HMPT $\Lambda_0 = 16{\cdot}4\ cm^2\ equiv^{-1}\ ohm^{-1}$			
2·552	340,000	14·4	0·910
5·103	175,000	13·9	0·892
25·52	50·400	9·68	0·646
51·03	26,500	9·19	0·634
510·3	3,900	6·12	0·483

TABLE 9. CONDUCTIVITY DATA FOR *sodio*-2-CARBETHOXYCYCLANONES IN DMSO AT 25·0°

$C \times 10^4$ mole/l	R ohms	Λ $cm^2\ equiv^{-1}\ ohm^{-1}$	α
Sodio-2-Carbethoxycyclopentanone (I-5) $\Lambda_0 = 42{\cdot}5\ cm^2\ equiv^{-1}\ ohm^{-1}$			
2·500	185,000	26·9	0·645
5·000	110,000	22·6	0·543
25·00	45,100	11·0	0·267
50·00	36,300	6·84	0·167
500·00	11,810	2·10	0·053
Sodio-2-Carbethoxycyclohexanone (I-6) $\Lambda_0 = 48{\cdot}4\ cm^2\ equiv^{-1}\ ohm^{-1}$			
2·555	179,000	26·7	0·563
5·110	113,000	19·8	0·416
25·55	58,000	8·38	0·175
51·10	50,500	4·82	0·103
511·0	14,400	1·68	0·038
Sodio-2-Carbethoxycyclooctanone (I-8) $\Lambda_0 = 48{\cdot}3\ cm^2\ equiv^{-1}\ ohm^{-1}$			
2·514	198,000	25·0	0·524
5·028	120,000	20·6	0·435
25·14	65,000	7·60	0·161
50·28	57,000	4·35	0·093
502·8	19,200	1·29	0·028

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