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THE EFFECT OF CROWN ETHERS ON THE ALKYLATION OF A CYCLIC β-KETO ESTER

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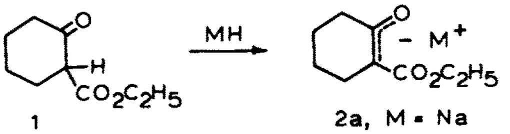
Abstract— The effects of crown ethers (**6** and **7**) on the reactions of sodium (**2a**) and potassium enolates (**2b**) of 2-ethoxycarbonylcyclohexanone (**1**) with isopropyl iodide in dimethylsulfoxide and dimethoxyethane have been investigated. When the addition of crown ether promoted dissociation of ion pair **2** in either of the two solvents, the total rate of reaction (k_t) increased and the ratio of carbon- (**3**) to oxygen-alkylation (**4** and **5**) products decreased. The results are consistent with the involvement of both the ion pair and more dissociated species in alkylation and with greater reactivity for the latter.

The regioselectivity of alkylation of an ambident anion depends on several factors[1,2] including the solvent,[2a-d] steric and electronic effects in the alkylating agent[2d,e] and anion,[2f,g] and the cation.[2b-d,h-j] Numerous systems have been studied, and correlations of regioselectivities with the above and other factors have been drawn.[1,2a,d] Rhoads *et al.* have demonstrated[2f,g] that the cation plays an important role in the course of C- and O-alkylation of enolates derived from a series of *cyclic* β-keto esters. The character of this role now has been investigated further with the use of crown ethers,[3] which have the ability to coordinate with cations and have been used in mechanistic studies of carbanion reactions.[4] Specifically, for sodium and potassium enolates **2**, derived from 2-ethoxycarbonylcyclohexanone (**1**), the effects of crown ethers[2b,c,j] and a cryptand[2j] on the alkylation of an *acyclic* with isopropyl iodide in dimethoxyethane (DME) and dimethylsulfoxide (DMSO) have been determined. Previously, Née and Tchoubar have reported[5] the effects of a crown ether and a cryptand on the alkylation of the related sodium enolate derived from 2-methoxycarbonylcyclohexanone with ethyl iodide and tosylate in 90:10 (molar) DMSO-methanol (Discussion). Others have previously investigated the influence of crown ethers[b,c,j] and a cryptand[2j] on the alkylation of an *acyclic* β-keto ester.

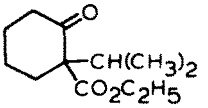
RESULTS

Enolates **2a** and **2b** were prepared by reaction of **1** with sodium and potassium hydride, respectively. Reaction of **2** with isopropyl iodide[6a] in DMSO or DME, with or without benzo-15-crown-5 (**6**) or 18-crown-6 (**7**), yielded C-alkylation product **3**, O-alkylation products **4** and **5**, and propene,[6b] formed in an elimination process with regeneration of **1**. It has been shown[7] that **5** is formed by isomerization of **4**. The ratio of C- to O-alkylated products (C/O) is defined as the molar ratio of **3**:(**4**+**5**), and C/O values were calculated on the basis of GC analyses of product mixtures. Runs for determination of C/O values were performed at 30.00±0.02° with 0.05 M solutions of **2** in DME and DMSO with and without an equal concentration of **6** or **7**, and values are compiled in Table 1.



1

2a, M = Na
b, M = K



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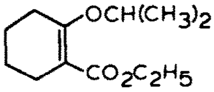

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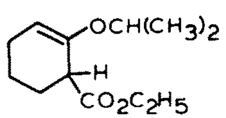

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Values of k_t, the second-order rate constant for disappearance of **2**, were measured at 30.00±0.02° for the reactions of **2a** with isopropyl iodide in DME and DMSO both with and without crown ether **6** and for those of **2b** with isopropyl iodide in DMSO with and without crown ether **7**. Uniformly, the initial concentration of **2** was held constant (0.05 M) to avoid complications from variation in the degree of ion pair dissociation with concentration, and when **6** or **7** was an additive, its concentration was also 0.05 M. In each run, the disappearance of **2** was followed titrimetrically, and k_t was evaluated from the least-squares plot of ln [isopropyl iodide]/[**2**] *vs* time. The second-order character of each reaction was indicated by the linearity of the rate plots and by the near invariance of k_t with different initial concentrations of isopropyl iodide. With the exception of those in DME,[8] each kinetic run was allowed to proceed through at least two half-lives. Rate data are summarized in Table 1.

Previously, Rhoads and Hasbrouck[2e] demonstrated that k_t represents the sum (eqn 1) of individual rate constants for C-alkylation (k_c, O-alkylation (k_o), and propene formation (k_p). For reactions of **2** in DMSO,

$$k_t = k_c + k_o + k_p \tag{1}$$

these rate constants were derived from values of k_t and GC product analyses as outlined in the Experimental, and they are listed in Table 2. For runs in DME, the accuracy of the data did not warrant such dissection of k_t values.

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Table 1. Summary of C/O ratios and rate constants for reaction of 2 with isopropyl iodide[a] at 30.00 ± 0.02°

Substrate[b]	Solvent	Crown Ether[c]	C/O[d]	k_t, L mol^{-1} sec^{-1} [e]
2a	DME	None	5.90 ± 0.07	7.7 ± 0.4 $\times 10^{-6}$
2a	DME	6	5.04 ± 0.07	55 ± 3 $\times 10^{-6}$
2a	DMSO	None	1.34 ± 0.02[f]	1.30 ± 0.02 $\times 10^{-3}$ [f]
2a	DMSO	6	1.33 ± 0.02	1.38 ± 0.04 $\times 10^{-3}$
2a	DMSO	7	1.33 ± 0.02	
2b	DMSO	None	0.73 ± 0.01	7.6 ± 0.2 $\times 10^{-3}$
2b	DMSO	7	0.62 ± 0.01	18.8 ± 0.5 $\times 10^{-3}$

[a] For C/O determinations, the concentration of isopropyl iodide was 0.20 M, and for kinetic runs, it was varied.[23] [b] For C/O determinations and kinetic runs, the concentration of 2 was 0.05 M. [c] In each case, the concentration was 0.05 M. [d] Defined as the ratio 3:(4 + 5); uncertainties are average deviations of multiple runs. [e] Uncertainties are average deviations of all runs[23] for a given combination of substrate, solvent, and crown ether, if added. [f] Rhoads and Hasbrouck[2g] reported C/O and k_t values of 1.34 ± 0.01 and 1.20 ± 0.01 $\times 10^{-3}$, respectively.

Table 2. Individual rate constants[a] for reaction of 2 with isopropyl iodide in DMSO at 30.00 ± 0.02°

Substrate	Crown Ether[b]	$k_c \times 10^4$, L mol^{-1} sec^{-1} [c]	$k_o \times 10^4$, L mol^{-1} sec^{-1} [c]	$k_p \times 10^4$, L mol^{-1} sec^{-1} [c]
2a	None	5.5 ± 0.5[d]	4.1 ± 0.4[d]	3.6 ± 0.3[d]
2a	6	5.8 ± 0.5	4.4 ± 0.4	3.4 ± 0.3
2b	None	28 ± 3	37 ± 3	10.2 ± 0.9
2b	7	67 ± 6	103 ± 9	19 ± 2

[a] Derived from k_t values of Table 1, and GC (and titrimetric) analyses of runs with 2 and isopropyl iodide concentrations of 0.05 and 0.20 M, respectively. [b] In each case, the concentration was 0.05 M. [c] Uncertainties based on combined maximum uncertainties for kinetic measurements and product analyses. [d] Rhoads and Hasbrouck[2g] reported k_c, k_o, and k_p values of 5.33 ± 0.23, 3.97 ± 0.16, and 2.70 ± 0.19 $\times 10^{-4}$, respectively.

Table 3. Dissociation fractions (α) for 0.05 M solutions of 2 in DMSO with and without 0.05 M crown ether at 30.00 ± 0.02°

Substrate	Crown Ether	α
2a	None	0.032[a]
2a	6	0.039
2b	None	0.136
2b	7	0.263

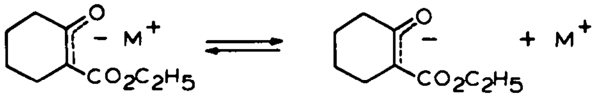
[a] Rhoads and Holder[2f] reported 0.038.

The conductivity in DMSO of 2 with and without crown ether was studied at 30.00 ± 0.02° to determine the extents of dissociation of the various alkali metal-enolate systems.[9] The method used to calculate the fraction of dissociation, α, was that of Forsbald[10] as applied by Rhoads and Holder.[2f] Dissociation fractions for 0.05 M solutions are recorded in Table 3.

DISCUSSION

In previous studies[2f,g] of 2a and its homologs in DMSO and hexamethylphosphoramide, it was concluded that dissociated enolate anions are more reactive than the corresponding ions pairs. This conclusion was based on observed solvent effects and on intersystem comparisons. In the present investigation, the use of crown ethers allowed the question of dissociated vs ion paired enolate anion reactivity for a given alkali metal enolate-solvent system to be examined *without* recourse to comparisons based on changes in solvent or enolate anion.

In DME, the addition of crown ether **6** effected a seven-fold increase in k_t for **2a** (Table 1). Crown ether **6** can form a complex[3] with Na^+, and in the weakly polar solvent DME the equilibrium represented by eqn(3) almost certainly lies to the right[11] (the encircled M^+ denotes the crown-complexed cation). Extensive complexation of M^+ by crown ether would shift the equilibrium of eqn(2) to the right, and the net result, (eqn 4), would be dissociation of metal enolate ion pair **2** into at least a crown ether-separated ion pair. Therefore, for **2a** in DME, the increase in k_t on addition of **6** can be attributed to enhanced ion pair dissociation and to a greater reactivity of the dissociated relative to the ion paired enolate anion.



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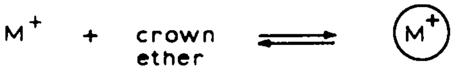
(2)



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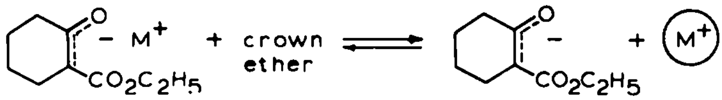

(4)

In DMSO, the addition of crown ether **6** had no effect on k_t for **2a**, whereas that of crown ether **7** increased k_t for **2b** (Table 1). In parallel results, the presence of **6** had no effect on the dissociation of **2a**, whereas that of **7** increased the dissociation of **2b** (Table 3). These facts are consistent with (1) the absence of any detectable effect of **6** on eqn(2) for **2a** in DMSO, which is in turn due to the lack of significant complexation of Na^+ by **6**, and (2) enhanced dissociation of **2b** (eqn 4) due to complexation of K^+ by **7** (eqn 3).[12] It can be concluded that in DMSO, as in DME, the dissociated is more reactive than the ion paired enolate anion.

The addition of crown ether **7** effected a modest decrease in the C/O ratio for **2b** in DMSO (Table 1). This result, coupled with the enhanced dissociation of **2b** in the presence of **7**, indicates that both the dissociated and ion paired enolate anion undergo alkylation. Likewise, the decrease in the C/O ratio for **2a** in DME on addition of crown ether **6** leads to an analogous conclusion. These facts are consistent with previous reports;[1,2b,c,f,j] generally, it is held that the C/O ratio for an ion pair is greater than that for the corresponding dissociated enolate anion. Neither the addition of crown ether **6** nor **7** affected the C/O ratio for **2a** in DMSO; this is consistent with the lack of complexation of Na^+ by crown ether (eqn 3). The greater value of k_t and smaller values of C/O for **2b** relative to those values for **2a** in DMSO are consistent with the greater dissociation of the former.[13]

For alkylation of sodio-2-methoxycarbonylcyclohexanone in 90:10 DMSO–methanol, Née and Tchoubar concluded[5] that both ion paired and dissociated enolate anions react with ethyl tosylate whereas essentially only the latter reacts with ethyl iodide. Direct comparison of the earlier[5] and present results for the two very similar cyclic β-keto ester systems is not possible due to differences in solvents and alkylating agents. However, taken together, the results suggest that in such an alkylation the relative reactivities of ion paired and dissociated enolate anions depend upon the precise natures of the alkylating agent and solvent. Therefore, generalizations about reactive species should be made with caution for alkylations of 2-alkoxycarbonylcyclohexanone enolates in particular, and of β-keto ester enolates in general. However, Reutov[2b,c] and Bram[2j] have investigated the influence of crown ethers and a cryptand on the alkylations of alkali metal enolates of ethyl acetoacetate with ethyl iodide and tosylate in a variety of solvents, and their results are uniformly consistent with the participation of both dissociated and ion paired enolate anions.

Finally, it is interesting to note that the rates of all three individual processes of **2b** in DMSO increased upon addition of crown ether **7** (Table 2). The increases in both k_c and k_o are consistent with the concept[2a] that dissociated and ion paired ambident anions both can undergo C- and O-alkylation and are inconsistent with the proposal[15] that C-alkylation involves only the ion pair. Elimination (k_p) accounts for 10% of the overall reaction (k_t) with, and 25% without crown ether **7**, and this enhancement of alkylation ($k_c + k_o$) relative to elimination on addition of **7** suggests that ion pair dissociation increases the nucleophilicity of the enolate anion more than its basicity.

EXPERIMENTAL

All m.ps and b.ps are uncorrected. The ^{1}H NMR spectra were recorded on a Varian HA-100 spectrometer in $CDCl_3$ with TMS as internal standard, and IR spectra on a Beckman Model IR-10 spectrophotometer using thin films of neat materials between NaCl plates. Conductance measurements were made with a Yellow Springs Instrument (YSI) Model 31 conductivity bridge equipped with a YSI Model 3403 conductance cell with a cell constant of 1.12 cm^{-1}. GC employed two columns: column A, 4 m × 1/4 in. aluminum packed with 10% Carbowax 1500 on 40–60 mesh AW DMCS Chromosorb W; and column B, 6 ft × 1/4 in. stainless steel packed with 3% SE 30 on 60–80 mesh Varaport 30. Both columns were used in a Varian Aerograph Model 2720 instrument with He as the carrier gas. A Lauda Model NBS constant temperature bath was used for C/O determinations, kinetic runs, and conductance measurements.

From LAH under N_2, THF and DME were distilled immediately before use. Hexane was distilled from LAH under N_2 and stored over 4 Å molecular sieves. For kinetic runs and C/O determinations, DMSO was distilled from CaO, and a center cut, b.p. 55–56° (0.05 mm), was redistilled (0.05 mm) from NaH. An additional distillation (0.05 mm) from NaH yielded DMSO used in conductance measurements.

2-Ethoxycarbonylcyclohexanone (**1**).[16] A standard procedure[17] yielded crude material which was distilled twice to give **1**, b.p. 54–57° (0.2 mm), lit.,[18] 107–109° (14 mm), which was >99% pure by GC analysis (column A, 140°, and B, 100°). This material was stored in the dark and redistilled at least every 2 months.

2, 3 - *Benzo* - 1, 4, 7, 10, 13 - *pentaoxacyclopentadeca* - 2 - *ene* (*Benzo* - 15 - *crown* - 5) (**6**) *and* 1, 4, 7, 10, 13, 16 - *Hexaoxacyclooctadecane* (18 - *Crown* - 6) (**7**). An established procedure[3] yielded crude **6**, and it was recrystallized five times from hexane to give **6**: m.p. 79.5–80.0°, lit.,[3] 79.0–79.5°. An established procedure[19] gave crude **7**, and it was sublimed twice at 80° (0.05 mm) to give **7**: m.p. 35–36°, lit.,[20] 39–40°.

Sodium enolate of 2 - *ethoxycarbonylcyclohexanone* (**2a**). A 250 ml 3-necked round-bottomed flask was equipped with a magnetic stirring bar, a gas inlet tube, a dropping funnel, and a fritted glass filter stick inserted through a rubber septum and attached through a trap and drying tube to a vacuum line. The oven-dried assembly was purged with dry N_2 for 30 min, and a net positive pressure of N_2 was maintained throughout subsequent operations. First, 0.26 g (0.011 mol) of NaH (57% dispersion in oil) was added to the flask, followed by 30 ml of hexane which was stirred and removed by vacuum through the filter stick. After two subsequent identical washings of the NaH, 75 ml of hexane was added. A soln of 1.87 g (0.0110 mol) of **1** in 75 ml of hexane was added dropwise to the stirred slurry of NaH at 25°, and the resultant mixture was stirred at 25° for 1 hr. Enolate **2a** was allowed to settle for 30 min, and solvent was removed through the filter stick. Then **2a** was washed three times with 150 ml portions of hexane, with each wash soln being removed as above. After **2a** was dried for 2 hr at 25° (0.05 mm), it was dissolved in 90 ml of solvent (DME or DMSO). The resultant soln was filtered by vacuum through a fritted glass funnel directly from the reaction flask into a100 ml volumetric flask and diluted to the mark to give a 0.1 M soln of **2a**.

Potassium enolate of 2-ethoxycarbonylcyclohexanone (**2b**). Into the dry and N_2-purged apparatus used for preparation of **2a** was added[21] 0.70 g (0.017 mol) of KH (35% dispersion in oil). It was washed with hexane using the above procedure for NaH, and 75 ml of THF was added. Then a soln of 3.25 g (0.0191 mol) of **1** in 75 ml of THF was added dropwise with stirring at 25°, and the resultant mixture was stirred for 1 hr at 25°. The THF was removed by flash distillation (0.05 mm) through an oven-dried distillation head, and residual **2b** was washed with hexane as was **2a** and dried for 2 hr at 25° (0.05 mm). The **2b** was dissolved in 100 ml of DMSO, and the soln was filtered into a 150 ml volumetric flask as in the preparation of **2a** and diluted to the mark to give a 0.1 M soln of **2b**.

General procedure for determination of C/O *values*. Isopropyl iodide (Aldrich), b.p. 80–81° (58 mm), was distilled three times from Na under N_2 and was stored over Ca in the dark.[22] All subsequent operations before completion of the reaction were performed under a protective N_2 atmosphere. A 0.40 M soln of isopropyl iodide in DMSO (or DME) and a 0.1 M soln of **2a** (or **2b**) in the same solvent were thermally equilibrated at 30.00 ± 0.02°. Then 10.0 ml of the enolate soln was pipetted into a 25 ml flask, which was protected from light with aluminum foil. In runs with crown ether, 0.268 g(1.00 mmol) of **6** or 0.264 g (1.00 mmol) of **7** was dissolved in the enolate soln. Then 10.0 ml of the iodide soln was pipetted into the enolate soln, and the resulting soln was swirled and placed in the constant temp. bath at 30.00 ± 0.02° for the appropriate time. Then the soln was poured into a mixture of 150 ml each of H_2O and hexane at 5°, and the system was shaken in a mechanical shaker for 45 min. The hexane layer was washed twice with 5 ml portions of cold H_2O, dried over 4 Å molecular sieves, and rotary-evaporated to leave the product mixture, which was analysed by GC (column A, 140°, 60 ml/min). Retention times were as follows: **1**, 20.0; **3**, 32.0; **4**, 34.5; and **5**, 18.5 min. GC integration (±3%) employed the trace, cut, and weight method with Keuffel Esser Co. Albanene 10–5351 tracing paper; the molar thermal conductivities of **1**, **3**, **4**, and **5** are equal.[2f,g] In the initial GC analyses, the product mixture was preparatively separated, and the identity of each component was established by comparison of its ^1H NMR and/or IR spectra with published values.[2g]

For each set of conditions, two parallel runs were made, and two GC analyses obtained for each run. In the determination of C/O values reported in Table 1, a reaction time of 300 min was used for runs with **2a** in DME, and times of 150 and 240 min for runs with **2a** and **2b**, respectively, in DMSO. The dissection of k_t values into their component rate constants (Table 2) employed data obtained as follows. For **2b** in DMSO with and without **7**, runs were allowed to proceed to completion, and the product mixture recovered after workup was analysed by GC. The mole fraction of **1** found in the mixture is equal to that of propene produced.[2f] For **2a** in DMSO with and without **6**, runs were not allowed to proceed to completion because decomposition of **4** and/or **5**, as detected by an increase in the C/O ratio, was observed in runs longer than 6 hr. Instead, the reaction was allowed to proceed for 150 min, at which time 9% of the original **2a** remained, as determined by titration in identical kinetic runs (*vide infra*). The product mixture recovered after workup was analysed by GC, and the integration data were corrected for the 9% of remaining **2a** to yield the mole fractions of **3**, **4**, **5**, and propene formed.

General procedure for kinetic runs. A 0.1 M stock soln of **2a** or **2b** in DME or DMSO was standardized by pipetting an aliquot into excess standardized 0.05 M HCl and back-titrating the mixture with standardized 0.05 M NaOH to a methyl purple end point. In runs with crown ether an equimolar amount of **6** or **7** then was added to the enolate soln. Stock solns of isopropyl iodide were prepared such that the concentrations were integral or half-integral multiples of the enolate concentration, and these and the enolate stock soln were thermally equilibrated at 30.00 ± 0.02° for 20 min. Then 25.0 ml of the enolate soln was added by pipet to a flask at 30.00 ± 0.02°, and with swirling, 25.0 ml of the isopropyl iodide soln was added likewise. Time zero was recorded when half of the iodide soln has been added, and the flask was sealed with a glass stopper. At appropriate time intervals, 5.0 ml aliquots of the added likewise. Time zero was recorded when half of the iodide soln had been added, and the flask was sealed with a glass stopper. At appropriate time intervals, 5.0 ml aliquots of the mixture were withdrawn by pipet, quenched with excess standardized 0.05 M HCl, and back-titrated with standardized 0.05 M NaOH to a methyl purple end point. Since the stoichiometry of the reaction between enolate and isopropyl iodide is 1 : 1, the concentration of the latter was calculated with the data from the titration. Six to eight points were taken for each run, and the second-order rate constants were determined from a least-squares plot of ln[isopropyl iodide]/[**2**] *vs* time. Data are summarized in Table 1.[23]

Conductivity of **2a** *and* **2b** *with and without* **6** *and* **7** *in DMSO*. Stock solutions (0.05 M) of freshly prepared **2a** and **2b** in DMSO were standardized as in the kinetic runs, and equimolar amounts of **6** and **7** were added as required. Appropriate dilutions gave solns with lower concentrations, and for each determination, seven solns were used from 0.0001 to 0.05 M. The degrees of dissociation, *α*, were determined using established procedures[2f,10] and are listed in Table 3.[25]

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