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THE EFFECT OF RING SIZE ON ACIDITY AND RATE OF C-ALKYLATION OF CYCLIC β-KETOESTERS[1]

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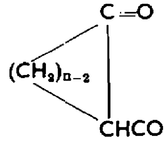
Abstract—A series of 2-carbethoxycyclanones of ring members 5–12 and 15 has been examined with respect to (1) the effect of ring size on $K_{eq.}$ for the reaction of sodium enolate formation with sodium ethoxide in ethanol and (2) the effect of ring size on the rate of alkylation of the sodium enolate by methyl iodide. The total acidities of the 2-carbethoxycyclanones as gauged by $K_{eq.}$ show a general decrease with increasing molecular weight, although a minimum at the 10-membered cycle is apparent when enol acidities are compared. The rates of alkylation show only a 10-fold range within the series and generally parallel the basicities of the enolate ions. Marked effects on acidity and alkylation rate which can be attributed to the presence of a cyclic structure are noted only for the five and six-membered ring systems.

For reasons set forth in the preceding paper[2] it was of interest to determine the effect of a systematic variation in ring size on the properties of carbanions of cyclic β-ketoesters as reflected in their basicities and their nucleophilicities. To this end, we have examined a series of 2-carbethoxycyclanones of five through 12 and 15 ring members (I-5, I-6, etc.) with respect to acidity and rate of C-methylation in an ethanol-sodium ethoxide system. For purposes of comparsion, the acyclic analogs, ethyl α-ethyl-acetoacetate, II, and ethyl 2-(n-hexyl)-3-ketodecanoate, III, were included in the study.



I-5, n = 5; I-6, n = 6; etc.

$CH_3COCH(C_2H_5)CO_2C_2H_5$

II

$CH_3(CH_2)_6COCH(C_6H_{13})CO_2C_2H_5$

III

The reaction scheme involved under the alkylation conditions used in this study may be represented in the general case by

$$HE + {}^{-}OEt \underset{\text{fast}}{\overset{K_{eq}}{\rightleftharpoons}} E^{-} + HOEt \qquad (1)$$

$$E^{-} + CH_3I \xrightarrow[\text{slow}]{k_1} E\text{–}CH_3 + I^{-} \qquad (2)$$

$$OEt^{-} + CH_3I \xrightarrow[\text{slow}]{k_2} EtO\text{–}CH_3 + I^{-} \qquad (3)$$

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[1] Abstracted from the Ph.D. Dissertation of A. W. D., University of Wyoming, June, 1962.

[2] S. J. Rhoads, J. C. Gilbert, A. W. Decora, T. R. Garland, R. J. Spangler and M. J. Urbigkit, *Tetrahedron* **19**, 1625 (1963).

where HE denotes a β-ketoester (and its enol) with an acidic hydrogen (pseudo-acid), E^-, the corresponding enolate ion, and $E\text{-}CH_3$, the α-methylated β-ketoester. Equation (3) represents the competing reaction of methyl ethyl ether formation.

In this work, the progress of the reaction was followed by measuring the consumption of total base, B_T, with time, where

$$B_T = (OEt^-) + (E^-) \tag{4}$$

The rate of disappearance of base is given by

$$-dB_T/dt = k_1(E^-)(CH_3I) + k_2(OEt^-)(CH_3I) \tag{5}$$

With the aid of equation (4) and the relationship

$$K_{eq.} = (E^-)/(HE)(OEt^-) \tag{6}$$

equation (5) may be transformed[3] into

$$-dB_T/dt = \left[\frac{k_1K_{eq.}(HE) + k_2}{K_{eq.}(HE) + 1}\right](B_T)(CH_3I) \tag{7}$$

Under the reaction conditions employed, the complexity of the kinetic behavior of these reactions is governed by the acidity of the substrate, HE. Two cases may be considered: I, when the β-ketoester, HE, is a sufficiently strong acid, the equilibrium shown in reaction (1) lies far to the right and the observed rate constant is equal to the alkylation constant, k_1; and II, when the ketoester is a relatively weak acid, the observed rate constant is a complex function of k_1, $K_{eq.}$, and k_2 and is given by the bracketed expression in equation (7). In the present study, both classes of β-ketoesters were encountered.[4] In the cases of those compounds showing the more complex kinetic pattern, k_1 was evaluated from $k_{obs.}$ and independently measured values of $K_{eq.}$ and k_2.

Equilibrium constants, $K_{eq.}$, *and acidities*

Concentration equilibrium constants, $K_{eq.}$, for the cyclic β-ketoesters, I-6 through I-12 and I-15, and for the acyclic compounds II and III were determined by conductance measurements of solutions of the *pseudo*-acids in ethanolic sodium ethoxide by the method described by Pearson.[3] The resistance data were treated by the method of Ballinger and Long.[5] These methods and typical calculations are described in detail in the experimental section of this paper. From the concentration equilibrium constants, $K_{eq.}$, and the ion-product for ethanol of $7{\cdot}28 \times 10^{-20}$ reported by Danner,[6] the acid ionization constants, K_a, of the β-ketoesters in ethanol were evaluated. These values are collected in Table 1. In the case of the five-membered ring β-ketoester, I-5, $K_{eq.}$ was estimated by a spectrophotometric method since this

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[3] See R. G. Pearson, *J. Amer. Chem. Soc.* **71**, 2212 (1949) for the completely analogous case of the alkylation of ethyl malonate.

[4] The two groups were easily distinguished by noting the effect on the observed rate constant of increasing the ester concentration relative to that of sodium ethoxide. The case I esters showed no change in rate constant with increasing (excess) ester concentration while for the case II esters the observed rate constant was increased by this change. See Experimental.

[5] P. Ballinger and F. A. Long, *J. Amer. Chem. Soc.* **81**, 1050 (1959).

[6] P. S. Danner, *J. Amer. Chem. Soc.* **44**, 2832 (1922).

TABLE 1. TOTAL ACIDITIES OF β-KETOESTERS IN ETHANOL AT 25°

β-Ketoester	$K_{eq.}$ [a]	$K_a \times 10^{18}$ [b]
Ethyl α-ethylacetoacetate	72 [c]	5·2
2-Carbethoxycyclopentanone	~9000 [d]	~650
2-Carbethoxycyclohexanone	416	30·3
2-Carbethoxycycloheptanone	100	7·3
2-Carbethoxycyclooctanone	154	11·2
2-Carbethoxycyclononanone	40	2·9
2-Carbethoxycyclodecanone	52	3·8
2-Carbethoxycycloundecanone	29	2·1
2-Carbethoxycyclododecanone	15	1·1
2-Carbethoxycyclopentadecanone	17	1·2
Ethyl 2-(n-hexyl)-3-ketodecanoate	11	0·8

[a] $K_{eq.} = (E^-)/(HE)(OEt^-)$. Determined by conductance method unless otherwise noted.

[b] $K_a = (H^+)(E^-)/(HE) = K_{eq.} \times (H^+)(OEt^-)$. Calculated using $7{\cdot}28 \times 10^{-20}$ for the ion-product of ethanol at 25°. Ref. 6.

[c] Measured at 30°.

[d] Determined spectrophotometrically. Unpublished work with R. J. Spangler. See R. S. Stearns and G. W. Wheland, *J. Amer. Chem. Soc.* **69**, 2025 (1947) for general procedure.

compound was far too strong an acid to be measured by the conductance method employed for the other compounds.

The values shown in Table 1 represent the *total* acidities of the tautomeric enol-keto systems present in these compounds. It is of interest to evaluate, at least roughly, the acidities of the individual tautomers, also. This may be done with the aid of the tautomeric equilibrium constants, K_T, reported by Schwarzenbach, *et al.*[7] for dilute ethanolic solutions of cyclic β-ketoesters of the same series. Table 2 summarizes

TABLE 2. KETO AND ENOL ACIDITIES OF CYCLIC β-KETOESTERS IN ETHANOL AT 25°

Ring carbons	K_T [a]	$K_E \times 10^{18}$ [b]	$K_K \times 10^{18}$ [b]
5	0·053	~13,000	~690
6	1·3	54	70
7	0·14	59	8·3
8	0·67	28	19
9	0·18	19	3·4
10	1·0	7·6	7·6
11	0·099	23	2·3
12	0·053	22	1·2
15	~0·04 [c]	~31	~1·2

[a] K_T = (enol)/(keto). Data of Schwarzenbach *et al.*, Ref. 7. The constants given refer to the ethyl esters of the 5, 6 and 7-membered ring compounds and the methyl esters of the higher ring systems.

[b] $K_E = (H^+)(E^-)/(\text{enol}) = K_a(1 + 1/K_T)$ and $K_K = (H^+)(E^-)/(\text{keto}) = K_a(1 + K_T)$ where $K_a = (H^+)(E^-)/(\text{enol} + \text{keto})$.

[c] Estimated from spectral data. Ref. 2.

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[7] G. Schwarzenbach, M. Zimmerman and V. Prelog, *Helv. Chim. Acta* **34**, 1954 (1951).

the keto (K_K) and enol (K_E) acidities evaluated from K_a and K_T. The variations in total acidity and in keto and enol acidities in the series are also shown graphically in Fig. 1 in which the pK's are plotted against the number of ring carbons. While no claim is made for the quantitative correctness of these estimations since the conditions for the evaluation of $K_{eq.}$ and K_T were somewhat different, it is clear from spectral studies of the cyclic β-ketoesters, I, and their acyclic counterparts, II and III,[2]

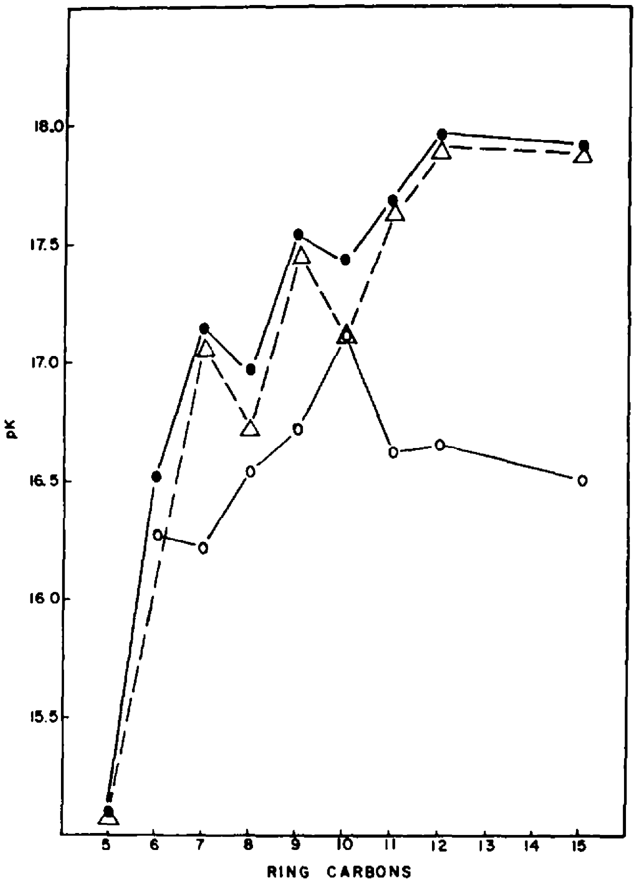

FIG. 1. Effect of ring size on total (●), keto (Δ), and enol (○) acidities of 2-carbethoxycyclanones.

that the values of K_T assumed here are of the correct order of magnitude and, therefore, that the trends in K_E and K_K in the series revealed in Table 2 and Fig. 1 are qualitatively valid.

The acidity data reveal several interesting facts. In terms of total acidity, it is apparent that it is only with the five and six-membered ring compounds that the presence of a ring structure exerts a pronounced acidity-enhancing effect. In general, the trend in the series is toward decreasing acidity with increasing molecular size. Moreover, the total acidities of the 7, 8, 9, and 10-membered ring β-ketoesters are comparable in magnitude to that of the open chain model, II, while the acidities of the cyclic ketoesters of 12 and 15 ring members compare with that of the acyclic analog, III. The five and six membered ring compounds are clearly exceptional, however; both are considerably more acidic than comparable open chain, α-substituted β-ketoesters and the five-membered cyclic derivative is some 20 times as strong an acid in ethanol as the six-membered ring compound.[8]

Deeper insight into the effect of ring size on acidity is afforded by a comparison of the individual tautomer acidities shown in Table 2 and Fig. 1. In contrast to the picture found when total acidities were compared, the acidities of the enolic species (K_E) in the series show a definite *minimum* with the 10- membered ring enol. The extraordinarily high acidity of the enol of the five-membered ring system is also remarked.[9] The contrasting values for the enol acidities in the five- and 10-membered ring systems suggest a marked difference in the stabilities of their chelated structures and correlate with the I.R. frequency differences noted and interpreted in the preceding paper.[2] The acidities of the ketonic species (K_K) in the series parallel the total acidities more closely but serve to accentuate the familiar alternating pattern so often observed when properties of medium ring compounds are compared.

The alkylation reactions and nucleophilicities

In order to obtain quantitative measures of the nucleophilicities of the carbanions of the cyclic β-ketoesters and their acyclic counterparts, it was necessary to evaluate k_1, the rate constant for the alkylation step (2) of the general scheme. Only the cyclic β-ketoesters of five and six ring members and ethyl acetoacetate were sufficiently strong acids to be largely converted to their anions under the reaction conditions employed (~0·1M NaOEt, reaction homogeneous throughout). For these β-ketoesters, $k_{\text{obs.}}$, evaluated from the second order plot of log $(CH_3I)/(B_T)$ *vs.* time, was constant and equal to k_1 over a range of methyl iodide concentrations and for β-ketoester-sodium ethoxide ratios greater than one.[10] Typical data are given in Table 6 of the Experimental. The alkylations were studied over a temperture range of 20° and activation parameters evaluated in the usual way. The rate constants at 30° and the activation quantities are summarized in Table 3.

For all the other β-ketoesters, the observed rate constant was found to increase with an increase in the β-ketoester-sodium ethoxide ratio. Therefore, the apparent second order rate constant, $k_{\text{obs.}}$, was obtained for several different initial concentrations of ester. Since the quantities of ester available were quite limited, the concentrations of ester used were usually such as to vary the observed rate constant by about 10 per cent. In order to evaluate k_1, the concentration of free β-ketoester, (HE), approximately half-way through the kinetic experiment was calculated from the previously determined value of $K_{\text{eq.}}$ and the concentration of base remaining at that time. Substitution of this value of (HE), together with the proper values for k_2,

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[8] We have not determined K_{eq}. for ethyl acetoacetate in ethanol but from reported K_a data in water it may be inferred that the acidity order is 2-carbethoxycyclopentanone > ethyl acetoacetate > 2-carbethoxycyclohexanone. R. G. Pearson and R. L. Dillon, *J. Amer. Chem. Soc.* 75, 2439 (1953).

[9] These differences in acidities noted when total and individual acidities are compared are, of course, the result of the fact that when two acids which ionize to form the same anion are at equilibrium, the weaker of the two will predominate in the mixture. The measurement of total acidity, then, tends to obscure the true acid strength of the less abundant tautomer.

[10] 2-Carbethoxycyclohexanone is actually a borderline case. Since the variation in $k_{\text{obs.}}$ with increasing ester concentration was barely detectable within experimental error, it has been treated as a case I ester. See Experimental.

$K_{eq.}$, and $k_{obs.}$ for a given kinetic run, into the expression

$$k_{obs.} = \left[\frac{k_1 K_{eq.}(\mathrm{HE}) + k_2}{K_{eq.}(\mathrm{HE}) + 1}\right] \tag{9}$$

permitted the calculation of k_1. The procedure is illustrated in the Experimental. In order to maintain homogeneity throughout the kinetic runs with the larger cycles it was necessary to resort to more dilute solutions of sodium ethoxide than were used for the smaller ring systems. Initial ethoxide concentrations of 0·05M sufficed for the medium ring compounds and 0·025M for the largest molecules. Alkylation rate constants were evaluated for all the β-ketoesters showing the complex kinetic pattern at four temperatures and the activation parameters obtained from the temperature dependence of the rates in the customary manner.[11] These values are also assembled in Table 3.

TABLE 3. RATE CONSTANTS AND ACTIVATION PARAMETERS FOR THE METHYLATION OF SODIUM ENOLATES IN ETHANOL AT 30°

β-Ketoester	$k_1 \times 10^3$ (l/mole-sec)[a]	$\Delta H^{\ddagger}$ (kcal/mole)[b]	$\Delta S^{\ddagger}$ (e.u.)[b]
Cyclic			
Ring carbons			
5	2·76 ± 0·05	15·5 ± 0·2	−19·1 ± 0·6
6	1·86 ± 0·02	16·8 ± 0·2	−15·6 ± 0·6
7	9·28 ± 0·12	14·9 ± 0·3	−18·6 ± 0·8
8	9·13 ± 0·15	14·7 ± 0·1	−19·4 ± 0·3
9	8·07 ± 0·08	14·6 ± 0·3	−20·0 ± 1·3
10	7·46 ± 0·06	15·7 ± 0·3	−16·4 ± 0·9
11	14·0 ± 0·4	16·1 ± 0·1	−13·9 ± 0·3
12	19·0 ± 0·9	15·3 ± 0·2	−16·0 ± 0·6
15	13·0 ± 0·4	15·0 ± 0·2	−17·7 ± 0·6
Acyclic			
Ethyl acetoacetate	2·42 ± 0·01	16·2 ± 0·3	−17·2 ± 1·1
Ethyl α-ethylacetoacetate	9·63 ± 0·03	15·5 ± 0·6	−16·8 ± 2·8
Ethyl 2-(n-hexyl)-3-ketodecanoate	17·6 ± 0·6	15·2 ± 0·3	−16·5 ± 0·8

[a] The values given are average values and deviations of at least two determinations.

[b] The uncertainties in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ were assessed by the method of E. L. Purlee, R. W. Taft, Jr. and C. A. DeFazio, *J. Amer. Chem. Soc.* **77**, 837 (1955).

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[11] It was assumed that $K_{eq.}$, determined at 25°, was essentially constant over the temperature range investigated. The validity of this assumption was tested in the case of 2-carbethoxycycloheptanone. The values of $K_{eq.}$ obtained at 25° and 40° for this compound were identical within experimental error (100 and 98).

The rate constant, k_2, for the competing reaction of methyl ethyl ether formation was independently determined in this work so that values of k_2 used in the calculations of the rate constants, k_1, would correspond to those characteristic of the conditions under which the alkylation studies were made.[12] These constants are summarized in Table 5 of the Experimental.

It should be pointed out that the sole product of the alkylation of all the β-ketoesters reported here was found to be the C-methylated derivative. Reaction mixtures from kinetic runs were carefully examined by g.l.p.c. analysis for any evidence of O-methylated products with negative results. It may safely be assumed, then, that the rate constants given in Table 3 refer to the C-alkylation process only.

Inspection of the rate data at 30° shows that there is a spread of only 10-fold in the rates of alkylation from the slowest, 2-carbethoxycyclohexanone, to the fastest, 2-carbethoxycyclododecanone. This range in rates corresponds to a difference in free energy of activation of only 1·3 kcal/mole. The data also reveal a general parallelism between the basicities and the nucleophilicities of the anions of the β-ketoesters. Thus, the "strong" acids, ethyl acetoacetate, I-5 and I-6, form anions of relatively low nucleophilic power; the β-ketoesters, ethyl α-ethylacetoacetate, I-7, I-8, I-9 and I-10, of intermediate acid strength, possess anions of moderate reactivity; while the "weak" acids, ethyl 2-(n-hexyl)-3-ketodecanoate, I-11, I-12 and I-15 furnish the most nucleophilic enolate ions. A test of the linearity of this relationship is shown in Fig. 2 in which log k_1 is plotted *vs.* pK_a.[13]

As Fig. 2 shows, the correlation between the basicities of the enolate ions as measured by pK_a and their nucleophilicities as gauged by log k_1 is only rough and the deviations from linearity imply that factors other than basicity are contributing to the nucleophilic properties of these ions. Recently, Edwards and Pearson[14] have discussed three factors which determine nucleophilicity, *viz.*, basicity, polarizability and the "alpha effect", arising from unshared electrons on an atom adjacent to the nucleophilic site. In the series at hand, however, in which the only variable in the structure of the nucleophile is the size of the ring, it must be assumed that the polarizability and alpha effect factors hold constant. The conclusion seems inescapable that the major factor which is responsible for the non-linearity of the basicity-nucleophilicity relationship is a steric one associated with conformational differences in the ring systems. However, these steric factors appear to play a relatively minor role in determining the energetics of the displacement reaction with methyl iodide as far as the ring systems above six members are concerned.

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[12] Brändström [A. Brändström, *Arkiv för Kemi* **11**, 567 (1957)] has shown that the observed rate constant of this reaction is dependent on the initial concentration of sodium ethoxide used; decreasing initial ethoxide concentrations produce increasing values of the rate constant. This behavior is attributed to the fact that the total reaction is a composite of ionic and ion-pair processes, the relative importance of which is a function of dilution. Such concentration dependence of rate constants and, presumably, of reaction mechanism, has also been observed for alkylation processes of the type studied in the present investigation. [See Brändström, *Arkiv för Kemi* **7**, 81 (1954); **13**, 51 (1958); *Acta Chem. Scand.* **7**, 223 (1953)]. It is for this reason that we have sought to maintain the same initial base concentrations in our rate studies.

[13] A more appropriate plot might have been log k_1 *vs.* pK_K because of the structural analogy. However, in view of the uncertainties associated with the estimation of K_K it seemed better to use the K_a values determined in this work. In any event, the K_K and K_a values are not vastly different.

[14] J. O. Edwards and R. G. Pearson. *J. Amer. Chem. Soc.* **84**, 16 (1962).

The five and six-membered ring compounds, however, clearly show an *inverse* relationship with respect to nucleophilicity and basicity. Thus, 2-carbethoxycyclopentanone, which is much the stronger acid of the two (by a factor of 20) yields a *more* nucleophilic enolate ion (by a factor of 1·5).[15] It is possible that this result can be rationalized in terms of the geometries of the two enolate ions and a difference in steric interactions in the transition states for their respective methylations. In the enolate ion of 2-carbethoxycyclopentanone, the cyclopentene-like ring is planar and the trimethylene moiety is held back from the nucleophilic site by angle strain forces in the ring. Such a structure offers minimal interference for the attack of the pi-electrons of the nucleophile on the substrate in the generalized S_N2 process. The enolate ion of the six-membered ring β-ketoester, however, would likely adopt a non-planar, *quasi*-chair conformation in which the two methylene groups at the "rear" of the ring (and above and below the plane defined by the other four carbons) would offer greater steric interference in the approach of this ion to the methyl iodide substrate than is the case for the five-membered cyclic ion. Such a steric factor would act in opposition to the intrinsically greater basicity of the six-membered

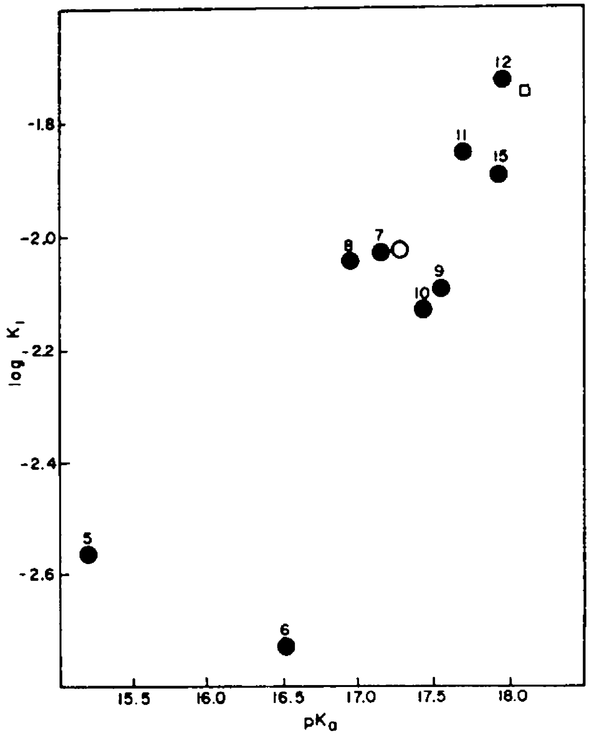

Fig. 2. Relationship between nucleophilicity and basicity of the anions of β-ketoesters.

●^{n}: 2-carbethoxycyclanones, where n = ring carbons
○: ethyl α-ethylacetoacetate
□: ethyl 2-(n-hexyl)-3-ketodecanoate

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[15] A similar, though less dramatic, inverse relationship is discernible for the 7- and 8-membered ring compounds in comparison with the 9- and 10.

ring enolate.[16] It is also quite possible that the sodium cation plays a role in these reactions and that this difference in nucleophilic reactivity may be traced to a difference in the relative importance of ionic and ion-pair (chelate) processes in displacement reactions for the two enolate systems.[17]

Examination of the activation quantities assembled in Table 3 shows that the smallness of the rate spread is due, in part, to compensating changes in $\Delta H\ddagger$ and $\Delta S\ddagger$. A test for the linearity of the $\Delta H\ddagger/\Delta S\ddagger$ relationship is shown in Fig. 3 where the areas about the points represent the uncertainties in the activation parameters.

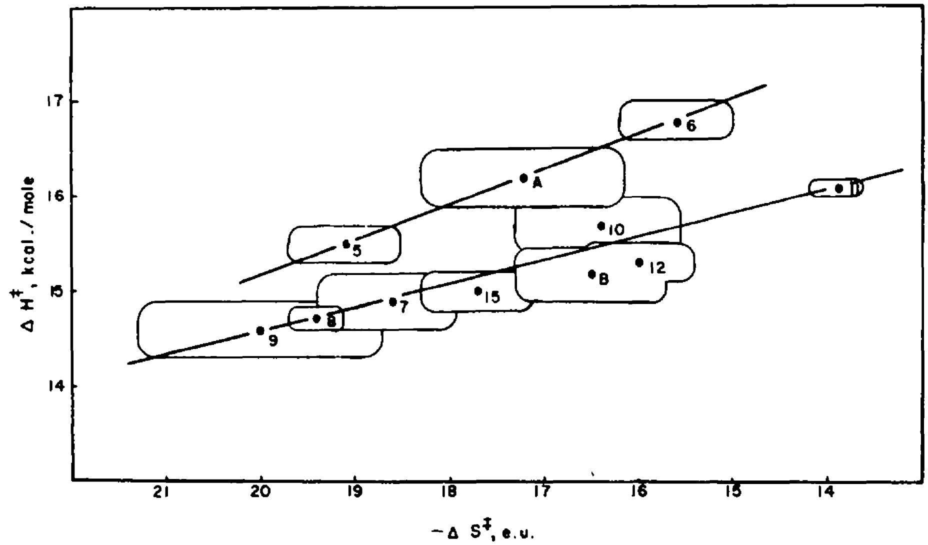

FIG. 3. Enthalpy-entropy relationship for reaction of C-methylation of β-ketoesters.
● ^{n}: 2-carbethoxycyclanones, where n = ring carbons
A: ethyl acetoacetate
B: ethyl 2-(n-hexyl)-3-ketodecanoate

It is seen that the points appear to define two straight lines of different slopes. One of these lines accommodates the "strong" acids, I-5, I-6 and ethyl acetoacetate; the other accommodates the weaker acids, I-7 through I-12, I-15 and its acyclic analog, III.[18] The slope of each line, corresponding to the isokinetic temperature,[19] was calculated by a least squares treatment of the data. The "strong" acids show an isokinetic temperature of 371°K and the weaker ones, an isokinetic temperature of 243°K.

According to Leffler,[19] the existence of two linear correlations suggests that the two groups of β-ketoesters react by different mechanisms or have appreciably different

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[16] This argument is somewhat similar to that put forth to explain the greater nucleophilic power of quinuclidine over that of triethylamine. H. C. Brown and N. R. Eldred, *J. Amer. Chem. Soc.* **71**, 445 (1949).

[17] See Ref. 12 as well as I. Forsblad, *Arkiv för Kemi* **13**, 349 (1958); **15**, 403 (1960); and N. Kornblum, R. Seltzer and P. Haberfield, *J. Amer. Chem. Soc.* **85**, 1148 (1963).

[18] Ethyl α-ethylacetoacetate was omitted from this treatment because of the relatively large uncertainties in its activation parameters.

[19] J. E. Leffler, *J. Org. Chem.* **20**, 1202 (1955). See also R. F. Brown, *Ibid.* **27**, 3015 (1962) for further discussion of the "Compensation Law".

transition states. Further, since the rate data were obtained below the isokinetic temperature for the "strong" acids, these reactions show "enthalpy control"; the rates for the second group of acids, determined above the isokinetic temperature, appear to belong in the "entropy-controlled" category. Any meaningful interpretation of this behaviour would require detailed information concerning the conformations of the enolate ions as well as the parts played by ion-pair processes in these reactions.[17]

The existence of two, rather discrete categories of reactions, however, serves as a warning that rather moderate changes in structure may significantly alter the reaction mechanism (or the position of the transition state along the reaction-coordinate) and that generalizations based on the seemingly similar systems are best avoided. It is noteworthy, that in the series at hand, the presence of a cyclic structure does not, *per se*, uniquely affect the reactivities of the carbanions in those cases in which the flexibility of the rings can be said to approach that of the structures of their open chain counterparts. In these reactions, the unusual effects of ring structure are confined to the relatively rigid five and six-membered cycles.

EXPERIMENTAL

Materials. The preparation and purification of the β-ketoesters used in this work were described earlier.[8] In all the work performed with these compounds, the ketoester was of the highest purity obtainable and a heart-cut of freshly distilled material was used. Analytical grade methyl iodide was carefully dried and distilled just prior to use. Anhydrous ethanol was prepared from commercial absolute ethanol according to the method described by Fieser.[20] The alcohol was maintained under anhydrous conditions prior to use and during handling. Stock solutions of sodium ethoxide were prepared by dissolving clean metallic sodium in anhydrous ethanol in volumetric flasks protected against atmospheric contamination. The sodium ethoxide solutions were standardized by delivering an aliquot into excess hydrochloric acid and back-titrating with standard sodium hydroxide to a methyl purple end point.

Determination of equilibrium constants, K_{eq}. The conductance apparatus used in this work consisted of a Leeds and Northrup Wheatstone bridge (Model 4760) set to read resistances of zero to 9999 ohms directly in steps of one ohm. A signal of 1000 c.p.s. at 8 volts was supplied by a Heathkit model AG-9A audio signal generator. The detector was a Heathkit model AV-3 audio vacuum tube voltmeter capable of measuring zero to 10 mv in its most sensitive region. The apparatus was equipped with a Wagner earthing device.[21] The precision and accuracy of the bridge were checked against a Leeds and Northrup model 4775 decade resistance box. In the range 100 to 9950 ohms, resistances could be determined within one ohm or less of the correct value and with a precision of about 0·1 %. A Freas-type conductance cell with lightly platinized plates and a total volume of 30 ml was used. The cell constant, determined with carefully prepared solutions of potassium chloride in conductance water was 0·322 cm^{-1}. The cell was maintained in a constant temp bath at 25·0 ± 0·05°.

In a typical determination, the resistance of a 0·015 M solution of sodium ethoxide was measured at 25° in triplicate and the average value taken as R_0. The 0·015 M solutions were prepared just before they were measured by dilution of a 0·15 M stock solution. The exact molarity of the 0·015 M solution was determined by titration immediately before the resistance was measured. At least three different quantities of β-ketoester were weighed directly into 50 ml volumetric flasks. The weights were chosen so that on dilution to volume the concentrations would be from three to 10 times the sodium ethoxide concentration. About 10 ml of anhydrous ethanol was added, followed by 5·0 ml of the same 0·15M sodium ethoxide stock solution used in the determination of R_0. After thorough mixing of the contents, the flask was placed in the constant temperature bath and final dilution was made at 25°. The base concentration of each solution was rechecked titrimetrically. The resistance, R, of each solution was measured at 25° after a period of no more than 15 min.[22]

[20] L. F. Fieser, *Experiments in Organic Chemistry* (3rd. Edition) p. 286 D. C. Heath, Boston (1955)

[21] G. Jones and R. C. Josephs, *J. Amer. Chem. Soc.* **50**, 1049 (1928).

[22] The measured resistances were not corrected for viscosity effects since the accuracy of the bridge did not allow detection of these small differences.

For the reaction

$$\underset{1-\alpha}{\mathrm{HE} + \mathrm{Na^+OEt^-}} \overset{K_{\mathrm{eq}}}{\rightleftharpoons} \underset{\alpha}{\mathrm{Na^-E^-} + \mathrm{EtOH}}$$

where α = fraction of sodium ethoxide converted to sodium enolate, the concentration equilibrium constant is given by

$$K_{\mathrm{eq.}} = \alpha/(\mathrm{HE})_{\mathrm{eq.}}(1 - \alpha) \tag{10}$$

and, provided that equivalent conductances are additive, the equivalent conductance of a solution of sodium ethoxide and β-ketoester in ethanol at equilibrium is given by

$$\Lambda_c = (1 - \alpha)\Lambda_c\mathrm{NaOEt} + \alpha\Lambda_c\mathrm{NaE} \tag{11}$$

where the Λ_c's are the equivalent conductances of sodium ethoxide and sodium enolate at the total electrolyte concentration, c, which is equal to the initial concentration of sodium ethoxide. Since the resistance of a solution is inversely proportional to the equivalent conductivity one may write

$$R/R_0 = \Lambda_c\mathrm{NaOEt}/[(1 - \alpha)\,\Lambda_c\mathrm{NaOEt} + \Lambda_c\mathrm{NaE}] \tag{12}$$

where R_0 is the resistance of a solution of sodium ethoxide of concentration, c, and R, the resistance of a solution of β-ketoester of an arbitrary initial concentration and sodium ethoxide of initial concentration, c.

The determination of α from the measured resistances requires a knowledge of the value of Λ_cNaE, the equivalent conductivity of a hypothetical solution of sodium enolate of concentration, c. This quantity may be approximated by the method of Pearson[9] in which a plot of $R/(R - R_0)$ *vs.* 1/HE is extrapolated to 1/HE equals zero. The extrapolation gives a value of R_∞ which is the resistance of a hypothetical solution of infinite β-ketoester concentration in which all of the sodium ethoxide has been converted to sodium enolate. The equivalent conductance, Λ_cNaE, may be calculated from the relationship, $\Lambda_c\mathrm{NaE} = 1000\,k/c\,R_\infty$, where k is the conductance cell constant and c is the concentration of sodium enolate.

A more accurate value of Λ_cNaE may be obtained by a graphical method based upon the interrelationships of $K_{\mathrm{eq.}}$, Λ_cNaE and α.[5] After the value of Λ_cNaE had been approximated by a Pearson plot of the resistance data, a number of arbitrary values in the vicinity of the approximate one were assigned to Λ_cNaE and corresponding values of α calculated from expression (12) from the data for a given solution of β-ketoester and sodium ethoxide. The values of α so obtained were used to calculate $K_{\mathrm{eq.}}$ from expression (10) corresponding to each arbitrary value of Λ_cNaE. A plot of the arbitrary values of Λ_cNaE against the corresponding values of $1/K_{\mathrm{eq.}}$ defined one straight line. Repetition of the process for each of the solutions measured gave a family of straight lines which intersected at or near a point corresponding to the best value of Λ_cNaE. This improved value of Λ_cNaE was then used to calculate α and finally $K_{\mathrm{eq.}}$. In this way, a self-consistent value of $K_{\mathrm{eq.}}$ was obtained for solutions of different initial ester concentrations. Data illustrative of these determinations are reproduced in Table 4. The examples shown are typical of the results for β-ketoesters of "strong", "moderate", and "weak" acid strengths.

Determination of rate constants: General Procedure. The reactions of alkylation of the β-ketoesters and of methyl ethyl ether formation were followed by titrimetric analysis for total base, B_T. Stock solutions of sodium ethoxide in anhydrous ethanol and methyl iodide in anhydrous ethanol were prepared in appropriate concentrations so that 20 or 25 ml of the solutions diluted to volume in a 50 ml flask would give the desired initial concentrations of these reagents. These standard solutions were maintained at the temperature characteristic of the particular kinetic run. For the determination of the rate of methylation of a β-ketoester, a sample of freshly distilled ester was weighed directly into a volumetric flask, a few ml of anhydrous alcohol was added, followed by the appropriate aliquot of standard sodium ethoxide solution and the combination was thoroughly mixed. The reaction flask was placed in the constant temp bath and the reaction started by the addition of the appropriate aliquot of methyl iodide standard solution.[23] Timing was started when the pipet was half-drained.

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[23] In some cases the order of addition of the methyl iodide and sodium ethoxide reagents was reversed. Test runs showed that this had no effect on the rate constants. The reverse order of addition was advantageous in those cases in which the sodium enolate had a low solubility.

Final dilution to volume was made with anhydrous alcohol and the contents of the flask were thoroughly mixed. All of these operations were carried out as rapidly as possible. Five ml aliquots of the reaction mixture were withdrawn periodically and delivered into excess standard hydrochloric acid solution to quench the reaction. Seven to nine aliquots were taken, usually in the range of 3–70% reaction. The excess acid was titrated with standard sodium hydroxide. Rate constants were evaluated from plots of log $(CH_3I)/(B_T)$ or, when appropriate, $1/(B_T)$, *vs.* time.

TABLE 4. EQUILIBRIUM CONSTANTS FOR THE REACTIONS OF THREE β-KETOESTERS WITH SODIUM ETHOXIDE IN ETHANOL AT 25°

β-Ketoester	$(NaOEt)_0$ m/l.	$(HE)_0$ m/l.	R ohms	α	$K_{eq.}$ l./m
2-Carbethoxy-cyclohexanone	0·00517	0·0	2030 = R_0		
		0·0106	4617	0·734	402
Λ_cNaE = 7·25 ohm^{-1} cm^2 [a]		0·0160	5525	0·828	414
		0·0200	5967	0·864	408
		0·0216	6124	0·880	428
		0·0296	6733	0·915	430
				Av	416
2-Carbethoxy-cyclodecanone	0·0153	0·0	858 = R_0		
		0·0310	1420	0·547	53
Λ_cNaE = 6·8 ohm^{-1} cm^2 [a]		0·0409	1552	0·627	54
		0·0710	1875	0·750	50
		0·0810	1961	0·778	51
		0·1012	2128	0·825	53
				Av	52
Ethyl 2-(n-hexyl)-3-ketodecanoate	0·0152	0·0	856 = R_0		
		0·0306	961	0·232	11
Λ_cNaE = 13·1 ohm^{-1} cm^2 [a]		0·0517	1019	0·341	11
		0·0712	1067	0·420	11
		0·1014	1127	0·511	11
		0·1413	1195	0·603	12
				Av	11

[a] Equivalent conductance of a hypothetical solution of sodium enolate in ethanol of concentration $c = (NaOEt)_0$. This is the improved value determined graphically. See text.

Determination of the rate constant, k_2. The rates of methyl ethyl ether formation at four temperatures were measured using 0·1M initial sodium ethoxide concentrations by the method described above except that the β-ketoester was omitted. The rate constants were corrected for lower inital ethoxide concentrations by applying proportionality factors derived from the data reported by Brändström.[12] The values of k_2 used in the present work are summarized in Table 5.

Effect of β-ketoester concentration on k_{obs}. The effect of an increase in the $(HE)_0/(NaOEt)_0$ ratio on the observed rate constant depends upon the magnitude of $K_{eq.}$ and upon the relative size of the rate constants, k_1 and k_2. This can be seen by letting $x = k_2/k_1$ and substituting xk_1 for k_2 in expression (9). Rearrangement gives

$$k_{obs.} = \frac{k_1[K_{eq.}(HE) + x]}{[K_{eq.}(HE) + 1]} \tag{14}$$

If $k_2 > k_1$, then $x > 1$ and $k_{obs.} > k_1$; if $k_2 < k_1$, then $x < 1$ and $k_{obs.} < k_1$; and, in the special case of $k_2 = k_1$, $x = 1$, and $k_{obs.} = k_1$. As (HE) is increased by increasing $(HE)_0$ relative to $(NaOEt)_0$, the observed rate constant always approaches k_1. This may involve either a *decrease* in $k_{obs.}$ (when $k_2 > k_1$) or an *increase* in $k_{obs.}$ (when $k_2 < k_1$). The magnitude of the effect of increasing $(HE)_0$ will

TABLE 5. RATE CONSTANTS FOR THE REACTION OF SODIUM ETHOXIDE WITH METHYL IODIDE AT FOUR TEMPERATURES

Temp °C.	$(NaOEt)_0$, m/l.	$k_2 \times 10^3$ l./mole-sec
20·0	0·100	0·812 ± 0·01
	0·050	0·893
	0·025	0·974
25·0	0·100	1·46 ± 0·05
	0·050	1·61
	0·025	1·75
30·0	0·100	2·58 ± 0·04
	0·050	2·84
	0·025	3·10
40·0	0·100	6·97 ± 0·06
	0·050	7·67
	0·025	8·36

be determined by the relative sizes of the terms in brackets in equation (14). When $K_{eq.}$ is large so that $K_{eq.}(HE) \gg x$ and 1, or when $x \cong 1$, the effect of increasing $(HE)_0$ is minor and, within experimental error, $k_{obs.} = k_1$. This situation is illustrated in the data for 2-carbethoxycyclopentanone ($K_{eq.}$ = 9000 and x = 1·07) and 2-carbethoxycyclohexanone ($K_{eq.}$ = 416 and x = 1·38) shown in Table 6. In the latter case, the values of $K_{eq.}$ and x combine to create a borderline situation in which a slight decrease in rate with increasing $(HE)_0$ is just discernible when 100% excess ester is used.[24] When $K_{eq.}$ is of the order of 100 or less, however, the effect of increasing $(HE)_0$ is easily detected. In all such cases encountered here, $k_1 > k_2$, so an increase in $(HE)_0$ is accompanied by an increase in k_{obs}. This may be seen in the data for ethyl α-ethylacetoacetate recorded in Table 6.

TABLE 6. EFFECT OF REAGENT CONCENTRATION ON OBSERVED RATE CONSTANTS OF SELECTED β-KETOESTERS AT 30°

β-Ketoester	$(HE)_0$ m/l.	$(NaOEt)_0$ m/l.	$(CH_3I)_0$ m/l.	$k_{obs.} \times 10^3$ l./mole-sec
2-Carbethoxycyclopentanone	0·0971	0·0971	0·0485	2·80
($K_{eq.} \simeq 9000$)	0·0973	0·0973	0·1947	2·81
	0·1947 [a]	0·0973	0·0973	2·83
2-Carbethoxycyclohexanone	0·0973	0·0973	0·0973	1·87
($K_{eq.}$ = 416)	0·0969	0·0969	0·2000	1·87
	0·1168 [b]	0·0973	0·0973	1·86
	0·1947 [a]	0·0973	0·0973	1·80
Ethyl α-ethylacetoacetate	0·0973	0·0973	0·0973	6·69
($K_{eq.}$ = 72)	0·1265 [c]	0·0973	0·0973	7·86
	0·1752 [d]	0·0973	0·0973	8·66

[a] 100% excess
[b] 20% excess
[c] 30% excess
[d] 80% excess

Treatment of the rate data

Evaluation of the rate constant, k_1. The alkylation rate constants, k_1, for the β-ketoesters whose rates were sensibly unaffected by an increase in the ester/ethoxide ratio were evaluated directly from

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[24] From the observed rate constants and $K_{eq.}$ of 416 for I-6, a refined value of 1·77 × 10^{-3} l./mole-sec. can be calculated for k_1, 5% lower than the value of 1·86 × 10^{-3} found by assuming $k_{obs.} = k_1$. Since this is barely beyond experimental error we have not applied this refinement.

rate data plots. These included ethyl acetoacetate, I-5 and I-6. Representative data are included in Table 6. Values for k_1 at various temperatures are summarized in Table 8.

The evaluation of k_1 for those β-ketoesters showing the more complex rate dependence was carried out in the following way. Initial concentrations of ester from 1·5–3 times the initial sodium ethoxide concentration and a methyl iodide concentration equivalent to the sodium ethoxide concentration were used. The reactions were followed by change in total base up to ca. 50% reaction. A plot of $1/(\mathrm{B}_T)$ against time for this first half-life showed very good linearity in all cases. The apparent second order rate constant, $k_{\mathrm{obs.}}$, was evaluated from this plot. The value of (HE) in expression (9) is the concentration of β-ketoester (corrected for that in the form of enolate ion) remaining at some time t, which was chosen approximately half-way through a kinetic experiment (i.e. at ~25% reaction) and is given by

Table 7. Sample data for the evaluation of k_1 for the methylation of 2-carbethoxycycloheptanone at four temperatures $(\mathrm{NaOEt})_0 = (\mathrm{B}_T)_0 = (\mathrm{CH_3I})_0 = 0{\cdot}0522$ M

Temp.	$(\mathrm{HE})_0$ m/l.	$(\mathrm{HE})_t$ [a] m/l.	$k_2 \times 10^3$ l./mole-sec	$k_{\mathrm{obs.}} \times 10^3$ l./mole-sec	$k_1 \times 10^3$ l./mole-sec
20·0	0·0913	0·0494	0·893	3·36	3·86
	0·1179	0·0714		3·47	3·83
	0·1563	0·1082		3·65	3·90
					Av 3·86 ± 0·02
25·0	0·0818	0·0360	1·61	5·29	6·31
	0·1045	0·0568		5·38	6·04
	0·1568	0·1071		5·74	6·13
					Av 6·16 ± 0·10
30·0	0·0910	0·0444	2·84	8·10	9·28
	0·1183	0·0699		8·63	9·46
	0·1587	0·1090		8·57	9·10
					Av 9·28 ± 0·12
40·0	0·0913	0·0433	7·67	18·9	21·5
	0·1179	0·0683		20·0	21·8
	0·1572	0·1065		20·3	21·5
					Av 21·6 ± 0·1

[a] These concentrations were calculated using $(\mathrm{B}_T)_t$ equal to 0·035, 0·030, 0·030, and 0·0265M for the temperatures 20°, 25°, 30° and 40°, respectively, and $K_{\mathrm{eq.}}$ equal to 100.

$$(\mathrm{HE})_t = (\mathrm{HE})_0 - [(\mathrm{B}_T)_0 - (\mathrm{B}_T)_t] - (\mathrm{E}^-)_t \tag{15}$$

Since

$$(\mathrm{B}_T)_t = (\mathrm{OEt}^-)_t - (\mathrm{E}^-)_t \text{ and } K_{\mathrm{eq.}} = (\mathrm{E}^-)_t/(\mathrm{OEt}^-)_t(\mathrm{HE})_t$$

the value of $(\mathrm{E}^-)_t$ can be calculated from known quantities through the relationship

$$K_{\mathrm{eq.}} = \frac{(\mathrm{E}^-)_t}{[(\mathrm{B}_T)_t - (\mathrm{E}^-)_t][(\mathrm{HE})_0 - [(\mathrm{B}_T)_0 - (\mathrm{B}_T)_t] - (\mathrm{E}^-)_t]}$$

Substitution of the value of $(\mathrm{E}^-)_t$ so calculated into expression (15) gives the desired $(\mathrm{HE})_t$. With this quantity and the measured values of $K_{\mathrm{eq.}}$, k_2, and $k_{\mathrm{obs.}}$, the rate constant k_1 may be evaluated from equation (9). Table 7 presents such data for a typical case, that of 2-carbethoxycycloheptanone at four temperatures. The alkylation rate constants for the other β-ketoesters of this class were evaluated in the same manner and are summarized in Table 8.

Arrhenius activation energies were obtained from plots of log k_1 *vs.* $1/T$ and the slope of the best straight line was calculated by a least squares treatment of the data. The activation enthalpies and entropies were evaluated for $T = 303{\cdot}1°$ K. from the relationships, $\Delta H^\ddagger = E_{\mathrm{act.}} - RT$ and $\Delta S^\ddagger = R \ln k_1 - R \ln (k'T/h) + \Delta H^\ddagger/T$. The statistical errors in $\Delta H^\ddagger$ and $\Delta S^\ddagger$ were evaluated using the

TABLE 8. SUMMARY OF ALKYLATION RATE CONSTANTS [a]

Compound	$k_1 \times 10^3$ l./mole-sec			
	20·0°	25·0°	30·0°	40·0°
I-5	1·15 ± 0·02		2·76 ± 0·05	6·63 ± 0·05
I-6	0·711 ± 0·02		1·86 ± 0·02	4·77 ± 0·06
I-7	3·86 ± 0·02	6·16 ± 0·10	9·28 ± 0·12	21·6 ± 0·1
I-8	3·89 ± 0·02	6·02 ± 0·04	9·13 ± 0·15	20·8 ± 0·4
I-9	3·11 ± 0·02	4·85 ± 0·05	8·07 ± 0·08	16·6 ± 0·03
I-10	3·19	4·95	7·46 ± 0·06	19·0
I-11	5·54	8·87	14·0 ± 0·4	34·2
I-12	7·67	12·5	19·0 ± 0·9	43·8
I-15	5·30	8·63	13·1 ± 0·2	29·5
III	7·17	10·6	17·6 ± 0·6	39·4
II		5·53 ± 0·09	9·63 ± 0·03	20·5 ± 0·01
Ethyl acetoacetate	0·874 ± 0·01	1·46 ± 0·01	2·42 ± 0·01	5·47 ± 0·05

[a] The values given represent average values and deviations of at least two kinetic runs except where no deviation is shown. In the latter cases, only single runs were made because of limited material.

formulas suggested by Purlee *et al.* (footnote *b*, Table 3). The precisions of the rate constants used in the calculation of these errors were estimated as the average deviations of the experimental rate constants from those calculated from the least squares equations.

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