

RATES OF ALKYLATION OF STRUCTURALLY
ISOMERIC LITHIUM ENOLATES OF 2-METHYLCYCLOHEXANONE

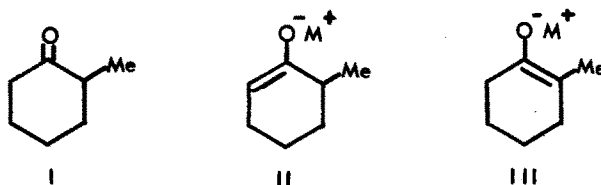
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The results of product studies have suggested that the less (II) and more (III) highly substituted metal enolates of 2-methylcyclohexanone (I) undergo alkylation at similar rates (1). However, kinetic studies on the rates of alkylation of these species have not been reported. We wish to report the results of our studies on rates of alkylation of kinetic and equilibrium mixtures of lithium enolates of I which suggest that III undergoes alkylation somewhat faster than II.

Using trityl lithium in 1,2-dimethoxyethane as the base and employing acetic anhydride quenching method (1, 2), kinetically prepared mixtures of lithium enolates of I showed a composition of 86% II and 14% III while enolate mixtures prepared under equilibrium conditions contained 10% II and 90% of III. Because these wide differences in enolate composition were obtainable and since lithium enolates of I (3) (and other unsymmetrical ketones (4, 5)) undergo alkylation with



reactive alkylating agents faster than enolate equilibration occurs, studies concerning the relative rates of alkylation of II and III appeared feasible.

The results of kinetic runs (6) are shown in Table I. The reactions of the lithium enolates of I with ethyl iodide and methyl *p*-toluenesulfonate in 1,2-dimethoxyethane proceed at rates which can be followed kinetically but rapidly enough so that significant enolate equilibration does not occur during the early stages of the reactions (7). In addition, during this period no polyalkylation is observed

Table I. Initial Rates of Alkylation of Kinetic and Equilibrium Mixtures of Lithium Enolates of 2-Methylcyclohexanone in 1,2-Dimethoxyethane at $25.10 \pm 0.01^\circ\text{C}$.

Alkylating Agent	Enolate Mixture	[Enolate] ₀ ^a	[RX] ₀ ^a	[Ketone] ₀ ^b	\bar{v} ^c
EtI	Kinetic	0.0324	0.224	~ 0.003	3.23
EtI	Equilibrium	0.0324	0.224	~ 0.003	4.91
MeOTs	Kinetic	0.0423	0.054	~ 0.004	2.78
MeOTs	Equilibrium	0.0400	0.054	~ 0.004	4.03
EtI(0.0°) ^d	Kinetic	0.0611	0.498	~ 0.005	2.98
EtI(0.0°)	Equilibrium	0.0612	0.498	~ 0.005	5.52

a. Initial molar concentration of reactants. b. Molar excess of 2-methylcyclohexanone added after trityl lithium decolorized. c. Initial rate = decrease in enolate concentration over first 20% reaction (based on the limiting reagent) in (moles/liter)/min. $\times 10^4$. d. Temperature maintained by a crushed ice-water mixture.

(7). Both the kinetic and equilibrium enolate solutions were prepared by titration of a solution of trityl lithium in 1,2-dimethoxyethane with I to a colorless end-point and then an additional 10% excess ketone was added (to eliminate catalysis by free ketone as a variable (8)). For the runs on kinetic mixtures the initial enolate concentration (9) was determined immediately and the alkylating agent was added. For the runs on the equilibrium mixtures the enolate solutions were refluxed for three hrs. (equilibration conditions) before determination of the initial enolate concentration (9) and addition of the alkylation agent. Using the lithium enolate mixture compositions and the data in Table I and solving equations 1 and 2 simultaneously, the initial rates of alkylation of the lithium enolates of I were calculated (Table II.)

$$(\%II) \left(\frac{v}{-II} \right) + (\%III) \left(\frac{v}{-III} \right) = \frac{v}{-kin.} \times 100 \quad (1)$$

$$(\%II) \left(\frac{v}{-II} \right) + (\%III) \left(\frac{v}{-III} \right) = \frac{v}{-eq.} \times 100 \quad (2)$$

Table II. Calculated Initial Rates of Alkylation of Lithium Enolates II and III in 1,2-Dimethoxyethane

Alkylating Agent	Temp.	$\frac{v}{-II}^a$	$\frac{v}{-III}^a$	$\frac{v}{-III}/\frac{v}{-II}$
EtI ^b	25.10°C	2.92	5.13	1.75
MeOTs ^b	25.10°C	2.59	4.19	1.62
EtI	0.0°C	2.51	5.85	2.33 ^c

a. (Moles/liter)/min. $\times 10^4$. b. It should be noted that a concentration of ethyl iodide approximately four times that of methyl p-toluenesulfonate gives roughly the same rate of disappearance of enolate. Our results suggest that alkyl iodides show greater reactivity relative to alkyl tosylates with lithium enolates of I in 1,2-dimethoxyethane than with sodium enolates of I in toluene (see ref. 11). This result appears to be consistent with recent studies of House and Trost (ref. 4). c. As expected the rate ratio at the lower temperature was greater than at 25.10°C.

Table II shows that the lithium enolates of I have similar alkylation rates (1) in 1,2-dimethoxyethane; the value of $\frac{v_{\text{III}}}{v_{\text{II}}}$ ranges from 1.62 to 2.33 depending upon the temperature and the alkylating agents employed. One of the factors involved in the reactivity of II and III is the influence of the methyl group at C-2. The inductive effect of this group should enhance the nucleophilicity and hence the reactivity of III compared with II. However, its steric influence might also retard the rate of alkylation of III in comparison with II (10). The small magnitude of the $\frac{v_{\text{III}}}{v_{\text{II}}}$ ratio suggests that these two opposing effects apparently are small or essentially cancel each other (11). Another salient factor which could be quite significant is the cation solvent shell-quasiequatorial methyl interaction in II (12, 13). As a result of this interaction a considerable amount of II having the C-2 methyl group quasiaxial probably exists in equilibrium with the conformer having this group quasiequatorial. The former species would be expected to be relatively unreactive with respect to its conformer and also to III in a stereoelectronically controlled axial alkylation (12). To the extent that the conformational equilibrium in II is forced toward the less reactive species (C-2 methyl quasiaxial), the concentration of the more reactive species would be reduced and the total rate of alkylation of II lowered (12).

The observed $\frac{v_{\text{III}}}{v_{\text{II}}}$ ratios and the variation of this ratio with temperature in the ethyl iodide case indicate that the activation energy for alkylation of III is apparently less than that for II. A combination of two factors appears likely — a small rate enhancement caused by the

presence of the C-2 methyl group on the double bond in III and/or the presence of a significant quantity of the less reactive conformer of II which suffers a relatively large reduction in reactivity at low temperature in accord with the expected high activation energy required for its alkylation.

Potassium and sodium enolates of I should have ratios of alkylation rates comparable to those of lithium enolates under similar conditions. Thus rapid enolate equilibration (3) and a slightly greater reactivity of III compared with II appear to be the major factors responsible for the predominance of 2,2-disubstitution products in alkylations of potassium and sodium enolates of I (1, 3). However, the preferential conversion of one of the monoalkylated products to polyalkylated material is also likely to be involved in product control (1).

Detailed kinetic studies on the alkylation of lithium enolates of I and related compounds are in progress.

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- (6) Aliquots of the reaction mixtures were hydrolyzed at various intervals and titrated with standard acid.
- (7) The products of the reactions of both the kinetic and equilibrium mixtures of lithium enolates of I with methyl *p*-toluenesulfonate and ethyl iodide were examined. The reactions were conducted under the same conditions as were employed for the kinetic runs in Table I and worked up after approximately 20% completion. Reaction of the kinetic mixture of enolates with methyl *p*-toluenesulfonate gave a mixture of products which was analyzed by a combination of v.p.c and n.m.r. spectroscopy as described previously (ref. 3) and found to contain 80% *cis*- and *trans*-2,6-dimethylcyclohexanone, 20% 2,2-dimethylcyclohexanone, and 0% 2,2,6-trimethylcyclohexanone. (We would have been able to detect easily as little as 2% of the trimethyl ketone in the mixture.) The same 2,6/2,2-isomer ratio was obtained on methylation of kinetic mixture of lithium enolates of I in 1,2-dimethoxyethane with excess methyl iodide. This demonstrated that no significant enolate equilibration occurs during the time period over which the initial alkylation rates were determined. V.p.c. analysis of the products from the reaction of the equilibrium mixture of enolates of I with methyl *p*-toluenesulfonate showed that only dimethylcyclohexanones were obtained in this case. In the reaction with ethyl iodide, product analysis by v.p.c. showed that neither the kinetic nor the equilibrium mixture of enolates of I gave any trialkyl products. In all cases authentic samples of dialkyl and trialkyl materials were used in the analytical procedures.
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- (9) Hydrolysis and titration of aliquots of the enolate mixtures before and after treatment with excess methyl iodide (the half-life of reaction of lithium enolates of I with methyl iodide is less than one min. under these conditions) gave the "total" and "extraneous" base concentrations, respectively. The initial enolate concentrations were obtained by difference.
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- (13) Employing protonation of enolates of 2,6-dimethylcyclohexanone (ref. 12) we have found this interaction to be about 0.75 kcal./mole in 1,2-dimethoxyethane for the lithium enolate case.