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RATES OF ALKYLATION OF METAL ENOLATES OF 2,6- AND 2,2-DIMETHYLCYCLOHEXANONE (1)

Drury Caine and Byron J. L. Huff (2)
School of Chemistry
Georgia Institute of Technology
Atlanta, Georgia 30332

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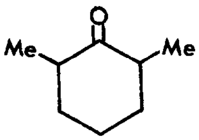
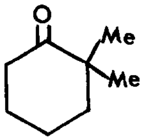
We have determined the rates of alkylation of the potassium and lithium enolates of 2,6-(I) and 2,2-dimethylcyclohexanone(II), that is, III and IV. The relative reactivities of these species and the manner in which the change in metal cation influences them is of interest in connection with the general problem of alkylation of metal enolates of cyclohexanone derivatives.



I



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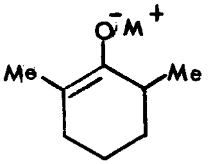
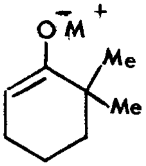


III



IV

a. C-2 methyl quasiequatorial
b. C-2 methyl quasiaxial

The kinetic results (see Table I) demonstrate that the lithium enolate IV reacts faster than its isomer III with excess ethyl iodide in 1,2-dimethoxyethane (DME) by a factor of 1.6. However, with the potassium enolates in DME and using n-butyl bromide as the alkylating agent, the order of reactivity is reversed and III reacts faster than IV by a factor of 2.8.

The enolate solutions were prepared by treating the ketones with trityl lithium or trityl potassium in DME, and these were assayed and the alkylation rates followed in a manner similar to that described previously for the lithium enolate of 2-methylcyclohexanone (3).

TABLE I

Rates of Alkylation of Metal Enolates of 2,6- and 2,2-Dimethylcyclohexanone.

Enolate	Metal	RX	[Enolate][a]	[RX][a]	Temp.	k[b]
III	Li	EtI	0.04800	0.5417	0.0°C[c]	4.288×10^{-4}
IV	Li	EtI	0.04800	0.5417	0.0°C[c]	6.913×10^{-4}
III	K	n-BuBr	0.04462	0.07964	29.95 ± 0.05°C	3.571×10^{-2}
IV	K	n-BuBr	0.04658	0.07964	29.95 ± 0.05°C	1.266×10^{-2}

a. Initial molar concentration of reactants. b. Second order rate constants in Liter/(Mole-sec). Each value is an average of two independent determinations.

c. Temperature maintained by a crushed ice-water mixture.

The specific alkylating agents were selected to give experimentally convenient alkylation rates. In all cases the calculated second order rate constants showed no significant variation over at least the first 30% of the reaction (4).

With a given metal the rates and hence the free energies of activation for alkylation with a particular alkyl halide are quite close for III and IV. In view of this it was felt that variations in ground state energy levels of the enolates could be partly responsible for the observed reversal in order of reactivity in going from lithium to potassium. Estimates of relative ground state stabilities of III and IV were obtained by treating a mixture of one equivalent each of I and II with one equivalent of trityl lithium or trityl potassium in DME, allowing equilibrium among the enolates to be established (5), and quenching the mixture with excess acetic anhydride (6, 7). V.p.c. analysis of the enol acetate mixtures (8) thus produced indicated that for the lithium case the III/IV ratio was 70:30, while in the potassium case it was 45:55 (9) (the greater stability of the more substituted lithium enolate in relation to the potassium one agrees with previous observations (10)). Indeed, in each case there appeared to be a correlation between enolate stability and reactivity in the alkylation reaction (11).

Depending upon the steric factors involved, the alkylation of a metal enolate of a cyclohexanone derivative can occur via a stereoelectronically controlled axial attack or via a non-chair transition state which allows continuous p-orbital overlap (12). In a chair-axial alkylation of IV, there exists a 1,3-interaction between the approaching alkylating agent and a quasiaxial methyl group at C-2. Considering this factor alone IV would be expected to be less reactive than III. It is true, however, that the difference might not be as large as expected. The solvent shell-quasiequatorial methyl interaction (13) in conformation IIIa causes III to exist to a substantial degree (ca 40% for both the potassium (13) and the lithium enolate (3) in DME) in conformation IIIb having the C-2 methyl group quasiaxial. This species would also be relatively unreactive in a chair-axial alkylation (13), and its presence in equilibrium with IIIa would lower the overall reactivity of III.

Examination of models suggests that the steric factors that would be involved in a non-chair alkylation of both conformers of III and of IV are quite similar. Thus, if this pathway alone were involved in alkylations of III and IV, reaction rates for the two enolates would be expected to be very close.

The presence of the methyl group at C-6 in III is an additional factor which influences the reactivity of III with respect to IV. The substituent could exhibit a rate retarding steric effect or a rate enhancing electronic effect by increasing the nucleophilicity of the carbon atom undergoing reaction. The data in Table I imply that these two factors essentially balance each other. However, the rate enhancing electronic effect appears to be slightly more important, particularly, in the potassium case.

The combination of (a) an enhanced nucleophilicity of carbon, (b) a more favorable situation for chair-axial alkylation, and (c) comparable ground state energies for the enolates III and IV are the factors which appear to be responsible for the more rapid alkylation of III in the potassium case. However, with lithium the first two factors noted above appear to be overshadowed by the higher ground state energy of IV so that it is more reactive than III.

The most interesting feature of the data is that for both metals the magnitude of the steric factor when a chair-axial alkylation is considered is apparently quite small. This suggests that the geometry of the transition state for the alkylation closely resembles that of the metal enolate, and that a transition state involving non-chair alkylation is readily accessible or actually preferred in these systems. Several other studies (12) and, particularly the work of Conia and Briet (14) on alkylations of potassium enolates of 2-alkyl-4-t-butylcyclohexanones, afford support for this point. It is surprising that although lithium enolates are much less reactive than their potassium counterparts, the transition states appear to lie very close to the reactants in both cases. The exact explanation for this must await further details of the mechanism of alkylation reactions.

Knowledge of the rates of alkylation of III and IV may be useful in predicting how polyalkylation influences product control in the alkylation of metal enolates of 2-methylcyclohexanone (6, 15). However, a number of factors in addition to the rates of reaction of III and IV must be considered in dealing with the polyalkylation problem. Further investigation of these is in progress.

References and Notes

1. This work was supported by a grant from the Petroleum Research Fund of the American Chemical Society.
2. NASA Trainee.
3. D. Caine and B. J. L. Huff, Tetrahedron Letters, 4695 (1966).
4. An aliquot from the reaction of IV (M=Li) with ethyl iodide was quenched after approximately 30% reaction and the ketone composition was determined by v.p.c. using a 10 ft. X 0.25 in. column containing 10% silicone SE-30 on Chromosorb W. Using an authentic sample of 2,2-dimethyl-6-ethylcyclohexanone (collected by preparative v.p.c. from the reaction mixture at infinite time) for comparison, it was found that at least 97% of the enolate consumed as determined by titration could be accounted for by the appearance of monoalkylated product. In a similar experiment involving ethylation of III (M=Li), again 97% of the enolate consumed as determined by titration led to monoalkylated product. Therefore polyalkylation, O-alkylation, and/or elimination in the lithium enolate alkylations is insignificant.

   The butylations of the potassium enolates III (M=K) and IV (M=K) were examined in a manner similar to that described above. Using a 5 ft. X 0.25 in. column containing 15% SF-96 on Chromosorb W for the v.p.c. analysis, it was found that in both cases at least 90% of the enolate consumed as determined by titration could be accounted for by the appearance of monobutylated product. Thus, although side reactions are apparently somewhat more important in the potassium than in the lithium enolate alkylations, the C-monoalkylation reaction is by far the predominant pathway in both cases.

5. In order to establish equilibrium among the metal enolates, the solution of the lithium enolates was refluxed for four hours and the solution of the potassium enolates was stirred for one hour at room temperature.

6. H. O. House and V. Kramar, J. Org. Chem., **28**, 3362 (1963).

7. H. J. Ringold and S. K. Malhotra, J. Am. Chem. Soc., **84**, 3402 (1962).

8. The enol acetates derived from I and II were separated on a 10 ft. X 0.25 in. column containing 20% Dow 550 silicone oil on Firebrick. These compounds exhibited the expected spectral properties and gave acceptable elemental analyses.

9. The relative ground state energies of III and IV at the temperatures of the kinetic runs differ slightly from these values because of the higher equilibration temperatures.

10. D. Caine, J. Org. Chem., **29**, 1868 (1964); H. O. House and B. M. Trost, ibid, **30**, 1341 (1965).

11. In our studies on the lithium enolates of 2-methylcyclohexanone (i) we found that the more substituted enolate, which is the more stable, exhibited an initial alkylation rate somewhat greater than its isomer (ref. 3). The data on III and IV suggest that steric and electronic factors should lead to a lower transition state energy for the more substituted than for the less substituted enolate of i, but that the difference in the transition state energies for the two species would probably not be as large as the difference in ground state energies. Presumably as a result of association and unlike III and IV in the same concentration range, in DME, mixtures of lithium enolates of i do not exhibit first order kinetics in enolate anion; the order approaches one at low concentration and zero at high concentration. Apparently, the degree of association of metal enolates is a sensitive function of structure and differences in the extent of association of the more compared with the less substituted enolate of i may, in part, account for the observed alkylation rate ratios.

12. See H. O. House, "Modern Synthetic Reactions", W. A. Benjamin, Inc., New York (1965), p. 202f and references therein.

13. S. K. Malhotra and F. Johnson, J. Am. Chem. Soc., **87**, 5513 (1965).

14. J. M. Conia and P. Briet, Tetrahedron Letters, 2797 (1964).

15. Ref. 12, p. 192.