THE RATES OF REDUCTION OF CYCLOHEXANONES WITH
LITHIUM TRI-t-BUTOXYALUMINOHYDRIDE

J. Klein and E. Dunkelblum

Department of Organic Chemistry, Hebrew University, Jerusalem, Israel

and

E. L. Eliel and Y. Senda

Department of Chemistry, University of Notre Dame, Notre Dame, Indiana, USA

The steric course of reduction of cyclohexanones with metal hydrides has been attributed[1] to the operation of two factors: a thermodynamic one related to the stability of the formed alcohols and a kinetic one. The first factor was called "Product Development Control" and was assumed to be dominant in unhindered ketones, and the second "Steric Approach Control" was thought to determine the course of reduction of hindered ones.

An alternate explanation[2], based on pure steric approach consideration was also put forward. More recently, eclipsing effects[3] were claimed to be responsible for preferential axial attack in unhindered ketones.

Our understanding of these reactions is hindered by the lack of kinetic data which would afford a comparison not only between two positions of attack in the same molecule but also between different ketones. Not even the kinetic order of the reduction with aluminohydrides is known. Possible complex formation between the reagents might affect our current views on the course of this reaction. Thus, an order of three halves in diborane[4], found in its reaction with cyclohexanones, was explained by complex formation.

Data are known for the kinetics of reduction of ketones with borohydrides[5] but not with aluminohydrides. Recently, competitive rate measurements between different cyclic ketones have been made for aluminohydrides[6]. It is possible, however, that competitive rates may not reflect the relative reactivity of the ketones, since they might be diffusion or mixing controlled.

We report the rates of reaction of lithium tri-t-butoxy-aluminohydride with 4-t-butylcyclohexanone (I), cis-3,5-dimethylcyclohexanone (II), 4-t-butyl-2,2-dimethyl-cyclohexanone (III), 3,5,5-trimethylcyclohexanone (IV) and 3,3,5,5-tetramethylcyclo-hexanone (V) (Table). Competitive rates[6] are included for comparison.

TABLE

|	Ketone	Conc. M ketone / LiAl(O-t-Bu)₃H	K_{ps}, sec	k, M⁻¹sec⁻¹	Average, k	Products, cis/trans	k_e, M⁻¹sec⁻¹	k_a, M⁻¹sec⁻¹	Relative rates[b] k_e/k_e^I	k_a/k_a^I
Fig. 1	I	0.005 A; 0.04	0.0502	1.26			0.13	1.27	1	1
		B; 0.06	0.0865	1.44	1.40					
		C; 0.08	0.119	1.49		9:91				
Fig. 2	II	0.005 A; 0.04	0.0354	0.89			0.11	0.88	1.09	0.09
		B; 0.06	0.0603	1.00	0.99	89:11				
		C; 0.08	0.0876	1.09						
Fig. 3	III	0.005 A; 0.04	0.0394	0.98			0.07	0.84	0.73	0.68
		B; 0.06	0.0526	0.88	0.91	8:92				
		C; 0.08	0.0777	0.97						
Fig. 4	IV	0.0125 A; 0.1	0.0075	0.075			0.075	0.009	0.44	0.003
		B; 0.2	0.0175	0.0875	0.084	11:89				
		C; 0.4	0.0355	0.0887						
Fig. 5	V	0.0125 A; 0.1	0.0049	0.049		—	0.052a)	—	0.35a)	—
		B; 0.2	0.0101	0.0505	0.052					
		C; 0.4	0.022	0.055						

a) Assuming $k_a = 0$.

b) From competition studies, Reference 6.

The rates were measured at 30° and 285 mμ by a spectrophotometric method[4], using a large excess of hydride. A plot of log A vs. time gave a straight line for all five ketones (figures 1-5) (A = C. D; D is the optical density and C — a constant). The reaction is therefore first order in ketone, $v = k_{ps}$ [ketone]. Each experiment was repeated three times and the points in the figures were taken at random from the experimental curves of all three runs. Variation of the concentration of the hydride has shown that the reaction is also first order in hydride $k = k_{ps} / [(t-BuO)_3 AlHLi]$. Determination by GLC of the rates of the formed isomers permitted to calculate the rate constant for axial (k_a) and equatorial (k_e) attack that give respectively the equatorial and axial alcohols. All these results are recorded in the table.

The kinetic results show that diffusion and mixing do not control the rates and that the calculation of k_a and k_e from the ratio of isomers[6] is therefore justified. The similarity of k_e for IV and I (or II) and of k for V (for which, presumably, $k_a \simeq 0$ and hence $k = k_e$) appears to rule out "product development" control which already appeared unlikely in the light of the observation[7,8] that the ratio of equatorial / axial alcohol formed from unhindered ketones such as I is higher than the corresponding equilibrium ratio. "Steric approach" control seems to be operative in the formation of the equatorial alcohol from IV which is slower by factors of 100 and 140 than the corresponding reaction of I and II. On the other hand, introduction of an axial methyl group at position 2 reduces k_e by only 45-36% (compare k_e for III with that for I or II) which makes unlikely the hypothesis[2] that steric approach factors are important in controlling the product ratio in the reduction of III. More likely, the outcome of this reduction is determined by Felkin's eclipsing factor[3]. It is of interest that an axial methyl at position 3 is much more effective in slowing axial attack on a cyclohexanone than is an axial methyl at position 2 in slowing equatorial attack.

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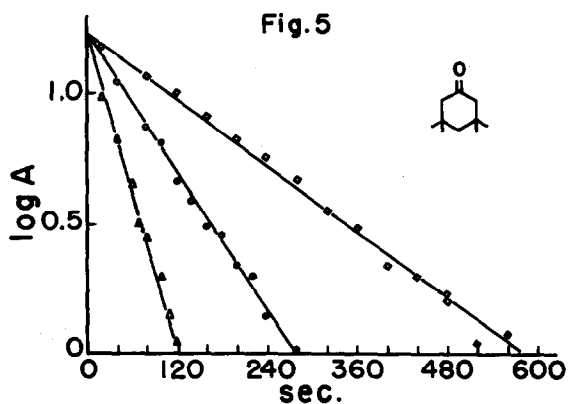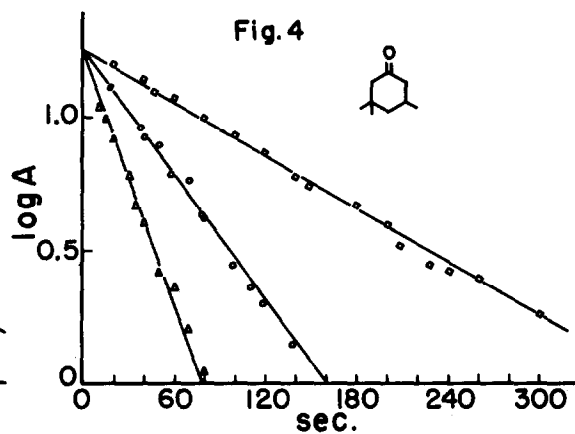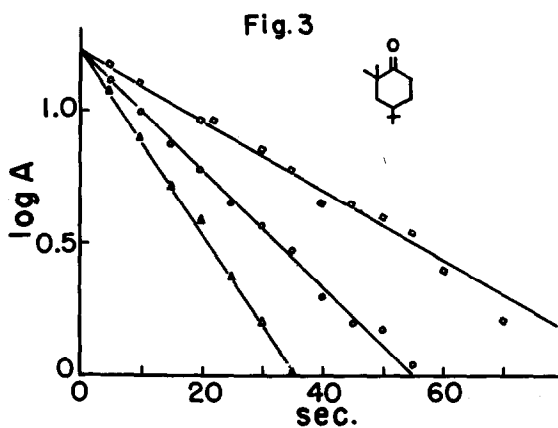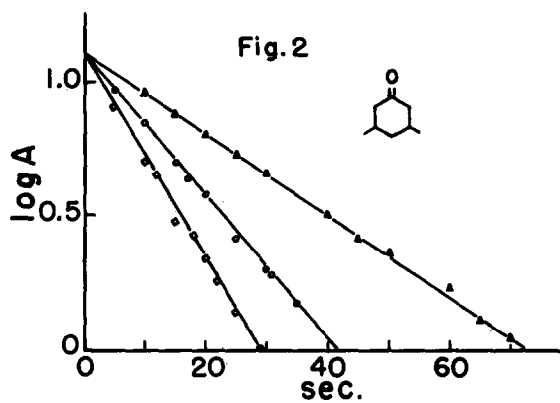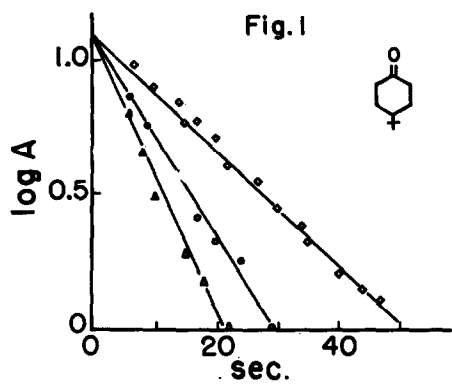
Kinetic Plots for
Reduction of I - V
With Lithium Tri-
t-butoxyalumino-
hydride.