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STERIC INTERFERENCE IN ALLYLIC AND PSEUDO-ALLYLIC SYSTEMS IV (1). LITHIUM-AMMONIA REDUCTION OF 3,4-DISUBSTITUTED-Δ^2-CYCLOHEXENONES, AND THE NATURE OF THE TRANSITION STATE

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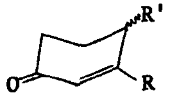
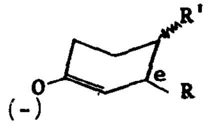
In 1954 Barton and Robinson (2) postulated that in the metal-ammonia reduction of α,β-unsaturated ketones, the β-carbon atom in the intermediate anion assumes considerable tetrahedral character, and its protonation leads to the formation of the thermodynamically more stable isomer. Stork and Darling (3), however, observed that in the β-carbanion protonation quite rigid stereoelectronic requirements have to be met, and they suggested that only those transition states are permitted in which maximum p-orbital overlap is maintained. Recently M. J. T. Robinson (4), after a careful study of the reduction of several $\Delta^{1(9)}$-2-octalones, has concluded that the product ratios may be accounted for if the transition state resembles the conformation of an intermediate anion in which the β-carbon atom is trigonal rather than to the product in which the β-carbon atom is tetrahedral.

In this paper we wish to report our findings regarding the lithium-ammonia reduction of 3,4-disubstituted-Δ^2-cyclohexenones represented by I. To our knowledge no systematic work has been reported in this particular area. The C-4 substituents in these ketones are largely axial since the alternate conformation with the equatorial C-4 substituent is destabilized by the $A^{(1,2)}$ strain between the C-3 and C-4 substituents (5,6). It was anticipated that if the transition state during the protonation resembles the intermediate anion in which the β-carbon atom is tetrahedral, the isomeric composition of the product would then reflect the thermodynamic stabilities of the enolate anions II and III. On the other hand if this carbon atom is trigonal, the product should then consist largely of the cis-isomer. The results presented in this paper however, now suggest that the β-carbon atom in the transition state may vary between these limits depending on the substituents present at C-3 and C-4.



Ia $(R,R'=CH_3)$
Ib $(R=CH_3;\ R'=C_2H_5)$
Ic $(R,R'=C_2H_5)$
Id $(R=C_6H_5;\ R'=CH_3)$
Ie $(R,R'=C_6H_5)$



II (R'=axial)
III (R'=equatorial)

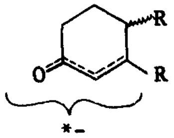
Each reduction was carried out by treating the ketone with an excess of lithium in liquid ammonia in the presence of ethanol. The resulting alcohol was oxidized by Jones' reagent (7) and the isomeric composition of the product determined by g.l.p.c. (8). The stereochemical assignment to the isomers was made by the Clemmensen reduction of the product to the corresponding cis- and trans-1,2-dialkylcyclohexanes (9), which were independently synthesized for the purpose of comparison (10). The results for the reduction of various ketones are given in Table I.

TABLE I

Ketone	% cis-isomer ±1	% trans-isomer ±1	$\Delta F^o = -RT \log_e \frac{cis}{trans}$ (Kcal/mole)[a]
Ia	16	84	+0.785
Ib	16.5	83.5	+0.765
Ic	56.5	43.5	-0.125
Id	94	6	-1.32
Ie	98	2	-1.87

(a) At -33°.

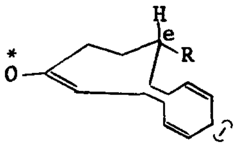
In the case of 3,4-dimethyl-Δ^2-cyclohexenone (Ia) the free energy difference between the corresponding enolate anions II and III $\approx$[1(1,3-diaxial CH_3/H interaction) + 1 (skew interaction between the C-4 methyl and the trigonal C-2 atom, i.e., 3-alkyl ketone effect)] (4,11) $\approx$ (0.9 + 0.4) = 1.3 Kcal., and if the β-carbon atom in the intermediate anion is tetrahedral, the product should be a 1:15 mixture of the cis- and trans-3,4-dimethylcyclohexanones (12). The formation of a 16:84 mixture of these isomers (ΔF° = 0.79 Kcal/mole) however, implies that the β-carbon atom in the transition state is not completely tetrahedral but has also a certain amount of trigonal character. This is definitely a consequence of the reflection of the inherent conjugation in the intermediate anion which may be represented by IV. We find a similar trend in the case of 4-ethyl-3-methyl-Δ^2-cyclohexenone (10) (1b). The pronounced increase in the proportion of the cis-isomer (56.5 ± 1%) in the case of 3,4-diethyl-Δ^2-cyclohexenone (10) (Ic) is however quite noteworthy (13). Further studied to assess the effect of substituent size on the nature of the transition state are in progress.



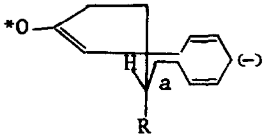
IV

(* denotes either one or two electrons)

The reduction of 3-phenyl-4-methyl-Δ^2-cyclohexenone (Id) (14) and 3,4-diphenyl-Δ^2-cyclohexenone (Ie) (15), on the other hand, led to overwhelming amounts of the corresponding cis-isomers. This may be attributed to the electron delocalization of the intermediate anion by the phenyl group leading to a resonance stabilized species V. Of the two conformers Va and Vb, the latter must by far be the more stable one since the former is destabilized by the severe $A^{(1,3)}$ strain (5,16) that exists between the equatorial C-4 substituent and the ortho -CH= of the C-3 benzene ring. An analogous case is found in the reduction of 3,4-diphenylcyclopentenone, which again led to the less stable cis-isomer (3). From this study we conclude that in the lithium-ammonia reduction of 3,4-disubstituted-Δ^2-



Va



Vb

cyclohexenones, the transition state resembles the conformation of an intermediate anion in which the β-carbon atom is not completely tetrahedral, but has a certain degree of trigonal character as well which may depend on the substituents at C-3 and C-4. The presence of an electron delocalizing group at the β-position, however, may introduce a considerable $A^{(1,3)}$ strain between the C-3 substituent and the equatorial C-4 substituent forcing the latter into the axial orientation.

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