Skeletal Rearrangements through Homoenolizable Methyl Groups in Acyclic Ketones. The Effect of Strain on the Regioselectivity of β-enolate Cleavage

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Summary Di-t-butyl ketone and 5,5,7,7-tetramethylundecan-6-one have been found to isomerize slowly under strongly basic conditions (Bu^{t}O$^-$–Bu^{t}OH, 185 °C), constituting the first examples of skeletal rearrangement through β-enolizable (homoenolizable) methyl groups.

While the generation of enolates by proton abstraction from the β- and γ-carbon atoms of ketones under strongly basic conditions has been examined in a variety of cyclic systems,[1] relatively little attention has been directed toward acyclic systems, although evidence of the intervention of β-enolates in these cases has been established.[2] Many of the cyclic systems exhibit skeletal rearrangements through β-enolizable methylene and methine carbon atoms as well as hydrogen–deuterium exchange at β-methyl carbon atoms but no examples of skeletal isomerization through β-enolizable methyl groups have been reported to date. Although exchange at β-methyl carbon atoms has been envisaged to proceed through β-enolates such as (**1**), the absence of an observed rearrangement (**1**) → (**2**) casts some doubt on the validity of (**1**) as an intermediate. It should be noted, however, that the β-methyl exchange process is stereoselective such that, for example, the three methyl groups of fenchone incorporate deuterium at distinctly different rates.[3] Thus, factors other than the inductive effect of the carbonyl group govern the reactivity of the β-methyl groups. Proof of the existence of species such as (**1**), however, would be welcomed and the isolation of the rearranged product (**2**) would accomplish this goal. We report that the acyclic ketones, di-t-butyl ketone (**3a**) and

5,5,7,7-tetramethylundecan-6-one (**3b**), under homoenolization conditions, rearrange slowly through (**4**) to (**5**).[4]

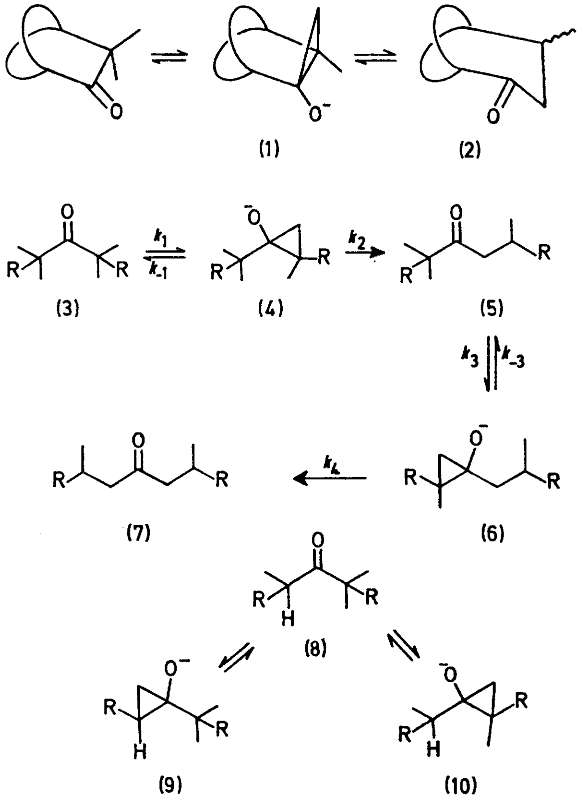
To a solution of $\mathrm{KOBu^t}$ in $\mathrm{Bu^tOH}$ ($[\mathrm{H_2O}] < 0{\cdot}005$ M), prepared by dissolving potassium metal in the anhydrous alcohol, was added (**3a**) giving a solution 0·2 M in ketone and 0·7 M in base. Aliquot portions were sealed in glass tubes under nitrogen and heated for various times at 185 °C. After recovery of the products by extraction into pentane (> 90% yields), g.l.c. analysis (DEGS and Carbowax 4000) revealed a minor component in addition to (**3a**), the amount of which increased with increased reaction times. After 150 h, 20% was present; the pseudo-first-order rate constant for its formation was found to be *ca.* $5 \times 10^{-7}\,\mathrm{s^{-1}}$. Preparative g.l.c. (Carbowax 4000) was employed to isolate this material which was shown (i.r., ^{1}H and ^{13}C n.m.r., and mixed m.p.) to be identical to t-butyl isobutyl ketone (**5a**). Treatment of (**5a**) under the same conditions led, after very long reaction times, to trace quantities (< 1%) of (**7**) *via* (**6**), as evidenced by g.l.c. analysis on three columns.

These experiments were repeated with $\mathrm{Bu^tOD}$ (99% deuteriated) as solvent and the amount of deuterium incorporation in recovered [$^{2}\mathrm{H}_x$]-(**3a**) samples was determined by mass spectrometry. This showed that k_{-1} = *ca.* $3k_2$. After similar experiments with (**5a**), analysis of the [$^{2}\mathrm{H}_x$]-(**5a**) samples by ^{2}H n.m.r. spectroscopy revealed that β-enolization of the t-butyl hydrogen atoms is competitive with enolization at the α-methylene position. Thus, for (**6**), $k_{-3} >> k_4$, in contrast to the partitioning found for (**4**).

A system capable of both rearrangement through β-enolizable methyl groups and more remote proton abstraction is 5,5,7,7-tetramethylundecan-6-one (**3b**), which was prepared by repeated methylation of the parent ketone with MeI–$\mathrm{NaNH_2}$, and was subjected to the homoenolization conditions.† After 70 h, the product contained 10% of a new compound, isolable by preparative g.l.c., shown to be a ketone, ν_{max} ($\mathrm{CHCl_3}$) 1710 cm^{-1}, and having a ^{13}C n.m.r. spectra containing fifteen signals. Off-resonance decoupling revealed five methyl signals: 14·0, 14·1, 20·0, and 24·3 (2); seven methylene peaks: 22·9, 23·4, 26·9, 29·3, 36·7, 39·7, and 44·4; one methine, 28·5; one quaternary, 47·6, and the carbonyl signal at 215·3 p.p.m. These data accord well with those expected for 5,5,8-trimethyldodecan-6-one (**5b**) and, upon $\mathrm{LiAlH_4}$ reduction, the product had identical g.l.c. behaviour on three columns to that of the authentic material prepared from 2,2-dimethylhexanal and 2-methylhexylmagnesium chloride. Experiments with (**3b**) conducted in $\mathrm{Bu^tOD}$ gave results analogous to those described for (3a), *viz.* k_{-1} = *ca.* $3k_2$. No deuterium was detected at positions other than the β-methyl carbon atoms, even after heating for several hundred hours at 185 °C.

Methylation of undecan-6-one gave the 5,5,7-trimethyl derivative (**8b**) readily and its behaviour under homoenolization conditions in $\mathrm{Bu^tOD}$ was also examined for competitive α and β enolization. The latter, in principle, can involve (**9b**) and (**10b**) and the ^{2}H n.m.r. spectra of [$^{2}\mathrm{H}_x$]-(**8b**) samples, obtained by g.l.c. after varying reaction times, clearly established that both possible β-enolates were formed. There was no evidence of skeletal rearrangement. Thus, the cleavage of (**9**) and (**10**) closely resembles that found for (**6**; R = $\mathrm{Bu^n}$).

These results not only provide additional examples of systems in which α and β enolization are competitive but also give further insight into the regioselectivity of β-enolate cleavage. Base-catalysed opening of cyclopropoxides favours the carbon atom which is more capable of stabilizing a negative charge.[5] Thus, cleavage toward a primary carbanion is expected to be greatly preferred over that to secondary or tertiary anions. This is exactly the behaviour found for (**6**), (**9**), and (**10**) but for (**4**), opening toward the tertiary centre is only slightly less favoured than that to the primary anion, *i.e.* k_{-1} = *ca.* $3k_2$. We suggest that the relative stabilities of (**3**) and (**5**) may be responsible. The carbonyl stretching frequency of (**3**) [ν_{max} ($\mathrm{CHCl_3}$) 1680 cm^{-1}], indicates a significant increase in the C–C–C bond angle which may destabilize (**3**) by 2—3 kcal mol^{-1}. A similar stability difference has recently been shown to give 100% regioselectivity in the homoketonization of 2-acetoxydeltacyclane[6] for which the two possible modes of cleavage involve carbon atoms with the same degree of alkylation. For (**4**), the two paths denoted by k_{-1} and k_2, involve carbon atoms with different substituents but we



a, R = Me
b, R = $\mathrm{Bu^n}$

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† This compound was identified by ^{13}C n.m.r., and i.r. spectroscopy and elemental analysis.

suggest that the greater exothermicity of the opening to (**5**) alters the regioselectivity, rendering the 'unexpected' mode of cleavage competitive with the regeneration of (**3**).

We thank the National Research Council of Canada for financial support, Professors J. P. Guthrie and D. H. Hunter for valuable discussions, and Ms. Marlene Brown for technical assistance.

(*Received*, 10*th June* 1976; *Com.* 659.)

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[1] A. Nickon, J. L. Lambert, J. E. Oliver, D. F. Covey, and J. Morgan, *J. Amer. Chem. Soc.*, 1976, **98**, 2593 and references therein.

[2] J. P. Freeman and J. H. Plonka, *J. Amer. Chem. Soc.*, 1966, **88**, 3662; P. Yates and M. J. Betts, *ibid.*, 1972, **94**, 1965.

[3] A. L. Johnson, J. B. Stothers, and C. T. Tan, *Canad. J. Chem.*, 1975, **53**, 212.

[4] The formation of (**4a**) had been suggested from the observation of hydrogen–deuterium exchange in (**3a**) when treated with $KOBu^t$ in Bu^tOD at 230 °C but no rearrangement was reported: D. J. Cram, 'Fundamentals of Carbanion Chemistry,' Academic Press, New York, 1965, p. 65.

[5] C. H. DePuy, *Accounts Chem. Res.*, 1968, **1**, 33.

[6] A. Nickon, D. F. Covey, G. D. Pandit, and J. J. Frank, *Tetrahedron Letters*, 1975, 3681.