Exclusive *syn*-Axial Alkylation of *O*-Methyl Oximes Resulting from an Orbital Symmetry Effect

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Summary Lithiation and subsequent methylation of several conformationally fixed oxime *O*-methyl ethers has been shown to give only one product resulting from axial attack at the α-carbon atom *syn* to the oxygen atom.

PREVIOUS work in this laboratory has shown that the reaction of lithiated nitrosamines (**1**) and (**2**) with MeI led solely to the *syn*-axial and diaxial methyl derivatives (**3**) and (**4**).[1] Since alkylation of cyclohexanones *via* their enolates generally exhibits little stereoselectivity,[2] we examined the lithiation and alkylation of the *O*-methyl oximes of 4-t-butyl cyclohexanone and several alkyl derivatives particularly with regard to stereochemistry. As anticipated, on the basis of the partial† isoelectronic nature of oximes and nitrosamines, we have found that oxime *O*-methyl ethers also show exclusive regio- and stereoselectivity, being converted into their *syn*-axial methyl derivatives without any other products being formed.[3]

Treatment of 4-t-butylcyclohexanone *O*-methyl oxime (**5**) with lithium di-isopropylamide (LDA) in tetrahydrofuran (THF) at −78 °C in the presence of hexamethylphosphoramide (HMPA), followed by the addition of MeI and warming the reaction mixture to room temperature gave the 2-methyl derivative (**6**)‡ in 94% yield. ^{1}H n.m.r. spectroscopy showed the presence of one product [⩾99·5%, since only 0·5% of the isomeric compound (**7**) was detectable in a prepared sample]. The stereochemistry of the methyl group in (**6**) was established as *syn* and *axial* by ^{13}C n.m.r. spectroscopy.§ All attempts to methylate (**6**) further failed. The isomerization of (**6**) to a mixture of (**6**), (**7**), and (**8**) was accomplished by heating in hexachlorobutadiene.[4] Methylation of a mixture of (**6**) and (**7**), after separation from (**8**) by column chromatography, gave the diaxial derivative (**9**) in a yield of 94% [based on the amount of (**7**) present as starting material]; methylation of (**8**) gave (**10**) in 86% yield. In both of these reactions no isomeric product could be detected by t.l.c. which was shown in a separate experiment to be sensitive to the presence of <0·5% of the isomer. Thus, in all three methylations of the conformationally fixed *O*-methyl oximes the alkylation is completely stereoselective and regioselective.

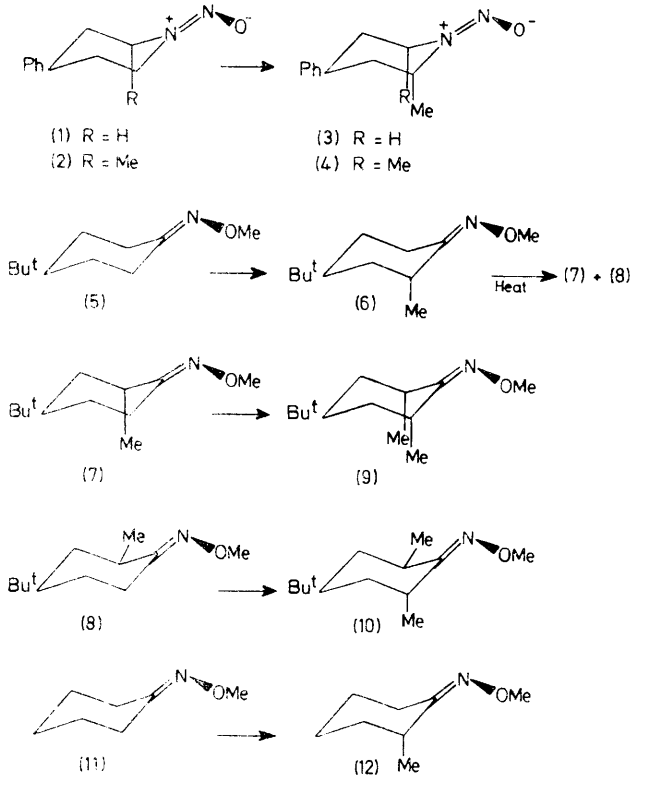
The origin of the preferential stabilization of an anion *syn* to the nitrosamino function has been investigated thoroughly.[5] The most probable explanation involves the symmetry properties of the nitrosamino carbanion which, like the butadiene dianion, derives stabilization from an

† The dipolar resonance structure, which contributes significantly to the overall electron distribution of nitrosamines, is isoelectronic with an *O*-alkyl oxime, *i.e.* >C=N–Ö:Me *vs.* >$\overset{+}{\text{N}}$=N–$\overset{-}{\text{O}}$:

‡ All new compounds gave satisfactory elemental analyses.

§ The ^{13}C n.m.r. spectra of all compounds studied herein revealed striking similarities to those already noted in nitrosopiperidines (R. R. Fraser and T. B. Grindley, *Canad. J. Chem.*, 1975, **53**, 2465) and oximes (G. E. Hawkes, K. Herwig, and J. D. Roberts, *J. Org. Chem.*, 1974, **39**, 1017) in that the *syn*-α-carbon atoms are considerably more shielded than their *anti* counterparts and an axial methyl group exerts an appreciable γ shielding effect.

attractive interaction between the termini of the four-atom π system when in the *syn* or *cis* configuration. Qualitatively speaking it is the symmetry of the HOMO of the



anion which is responsible for the effect. This rationale, originally used by Hoffmann and Olofson[6] to account for the unusual stability of *cis* dihalogeno- and dialkoxy-ethylenes, has been expanded quantitatively by Epiotis.[7] Recently the same orbital symmetry argument was put forward to account for a marked *syn* selectivity found in the H–D exchange of the *O*-methyl oxime of dibenzyl ketone.[8]

A number of investigators have attributed the predominant formation of *syn*[9] or *cis*[10] products from anionic intermediates to the chelation of the cation between the two termini of the 4π-system. This possibility has been excluded as an explanation for preferential H–D exchange of the *syn* protons (10^3 faster than *anti*) in a rigid nitrosamine,[5] by showing that, during exchange in the presence of a crown ether, the selectivity was not altered. We have applied the same test of mechanism to the methylation of the *O*-methyl oxime of cyclohexanone (**11**).¶

Methylation of (**11**) under the same reaction conditions and with the same analytical methods as used for (**5**) gave a single product (**12**) in 84% yield. Repetition of the reaction in the presence of 1·2 equiv. of 15-crown-5 again gave only the *syn* isomer. Since cation involvement is likely to be precluded by the presence of the crown ether,[11] the *syn* selectivity can most reasonably be attributed to the effect of orbital symmetry.

This *syn* stabilization is, in turn, responsible for the exclusively axial course of methylation in the fixed systems.** It has been established that there is a destabilizing interaction (A^1† strain) of at least 4·1 kcal mol^{-1} between the oxygen atom of the nitrosamino group and a methyl substituent in the α-equatorial position.[1] By comparison an α-axial methyl group was shown to have only 1·9 kcal mol^{-1} of strain. Even the diaxial *N*-nitroso-2,6-dimethyl-4-phenylpiperidine was at least 1·4 kcal mol^{-1} more stable than the isomer with a *syn*-equatorial methyl group. Thus A^1† strain, coupled with an appreciable influence of stereoelectronic control, accounts for the axial stereoselectivity in the methylation of nitrosamines, and presumably also in the methylation of *O*-methyl oximes.

Preliminary results indicate this *syn*-axial selectivity extends to the alkylations of 4-t-butylcyclohexanone *NN*-dimethylhydrazone[12] and also to other electrophilic reactions of lithiated *O*-methyl oximes and hydrazones.

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¶ The choice of (**11**) as the substrate in this test was based on the proven ability of both ^{1}H n.m.r. spectroscopy and t.l.c. to detect 0·5% of the *anti* isomer of (**12**).

** Formation of axial product *via* equatorial attack and equilibration is considered unlikely since the requisite anionic intermediate is much less stable, as indicated by our inability to form it, *i.e.*, the methylation of (**6**) failed.

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[3] Although alkylation of *O*-methyl oxime anions has not been investigated previously, a report of their conversion into $\alpha\beta$ unsaturated ketones recently appeared (V. Jager and H. Grund, *Angew. Chem. Internat. Edn.*, 1976, **15**, 50). Alkylation of oxime dianions, first reported by Hauser's group (C. F. Beam, M. C. D. Dyer, R. H. Schwarz, and C. R. Hauser, *J. Org. Chem.*, 1970, **35**, 1806), are now reported to exhibit high *syn* selectivity (W. G. Kofron and M.-K. Yeh, *J. Org. Chem.*, 1976, **41**, 439, attributed to chelation, and M. E. Jung, P. A. Blair, and J. A. Lowe, *Tetrahedron Letters*, 1976, 1439, attributed to orbital symmetry. No axial–equatorial ratios were examined).
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[11] C. J. Pedersen and H. K. Frensdorff, *Angew. Chem. Internat. Edn.*, 1972, **11**, 16.
[12] Extensive studies on the reactions of ketone *NN*-dimethylhydrazones have been described recently; E. J. Corey and D. Enders, *Tetrahedron Letters*, 1976, **3**. The alkylation of 4-t-butyl cyclohexanone *NN*-dimethylhydrazone was reported without any discussion of stereochemistry.