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DIRECTING EFFECT OF A NEIGHBORING HYDROXYL SUBSTITUENT ON BASE-CATALYZED ENOLIZATION OF A KETONE†

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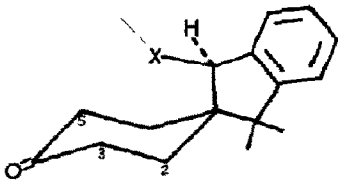
Abstract: Evidence is presented that a neighboring hydroxyl substituent may exert a directing effect on the base-catalyzed enolization of a cyclohexanone derivative.

We are engaged in a study of proximity effects on enolate-mediated reactions of carbonyl compounds using α-H,D exchange as the probe reaction. Our substrates are spirocyclic 6-membered ketones of the type 1 in which (a) the carbonyl group lies in the plane of symmetry of the skeletal framework of the molecule and (b) the environment of the carbonyl group is rendered asymmetric due to the spacial proximity of a second functional group X. Our initial experiments were performed with hydroxy-ketone 2 and have disclosed that monodeuteration is unexpectedly rapid and leads selectively to replacement of the 3[axial]-hydrogen by deuterium.



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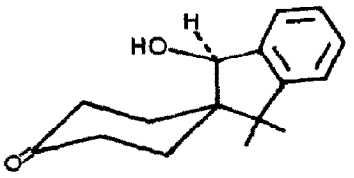

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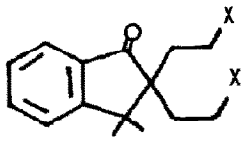
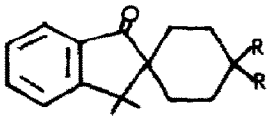
Compound 2 was synthesized by the following seven step sequence which was accomplished in 57% overall yield. The base-catalyzed reaction of 4,4-dimethyl-1-indanone[1] and acrylonitrile gave dinitrile 3[2], m.p. 124-124.5°, which was converted (HCl/CH_3OH) to the corresponding diester 4[2], m.p. 111-112°. Dieckmann cyclization ($NaOCH_3$/benzene) followed by decarbomethoxylation[3] (NaCl, H_2O, DMSO, 165°) produced diketone 5[2], m.p. 127-128.5°. The latter, with CH_3OH, $HC(OCH_3)_3$, and H_2SO_4 gave monoketal 6, an oil, which was reduced ($LiAlH_4$) to hydroxyketal 7[2], m.p. 73.5-75°. This product was prone to carbon skeleton rearrangement under acidic conditions but treatment with picric acid in a water-chloroform medium accomplished deketalization and gave 8[2], m.p. 114-115°.

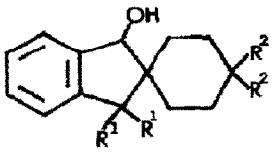
†This paper is dedicated to the memory of Professor Robert Burns Woodward.



3 X = CN
4 X = CO_2CH_3



5 R,R = O
6 R = OCH_3



7 R^1 = CH_3, R^2 = OCH_3
8 R^1 = CH_3, R^2, R^2 = O
9 R^1 = H, R^2, R^2 = O

Hydroxyketone 8 (≡ 2) was found to undergo rapid incorporation of carbon-bound[4] deuterium when dissolved in CH_3OD in the presence of Et_3N as catalyst. Deuterium incorporation was followed by mass spectrometry and extensive kinetic studies of deuterium uptake were performed at $30.0\pm0.1^\circ$ with Et_3N concentrations varying from 5×10^{-4} M to 10^{-2} M. Excellent pseudo-first order kinetics were obtained in all cases.[5] For the present purposes, the most significant finding was that the first carbon-bound deuterium was incorporated 35 times faster than the second deuterium after statistical correction. (The second deuterium was incorporated somewhat faster than for an α[axial]hydrogen of 4-t-butyl-cyclohexanone under the same conditions.) On the basis of these results, we were able to determine the optimum experimental conditions for a preparative experiment which would furnish a sample with maximum d_1 -content for spectral analysis. The deuteration of 2 was performed for 18 hr. at 30° in CH_3OD containing Et_3N at 0.001 M concentration. The product consisted of 23% d_o, 70% d_1, and 7% d_2 species. In order to determine the location of the deuterium substituent in the predominant d_1 species it was first necessary to analyze the proton nmr spectrum of the parent hydroxyketone 2.

In $CDCl_3$ solution, the cyclohexanone ring protons of 2 are not individually distinguishable but are represented by a complex of overlapping multiplets between δ 1.5 and δ 3.0. However, the addition of a lanthanide shift reagent (LSR), Eu $(fod)_3$, in small increments led to a series of shifted spectra in which most of the protons were individually visible. These spectra provided chemical shift data which, when extrapolated to zero LSR concentration, gave unshifted resonance positions (δ_{CDCl_3}) for the various protons. This information, along with the observed splitting patterns, led to the identification of all non-aromatic protons. Chemical shifts for the four α-protons of 2 are given in Table 1. Paramagnetic induced shift

	δ_{CDCl_3}	-ΔEu
3[axial]	2.74	15.6
3[equat.]	2.41	11.4
5[axial]	2.58	12.6
5[equat.]	2.37	10.4

Table 1

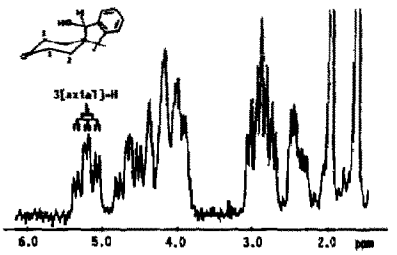
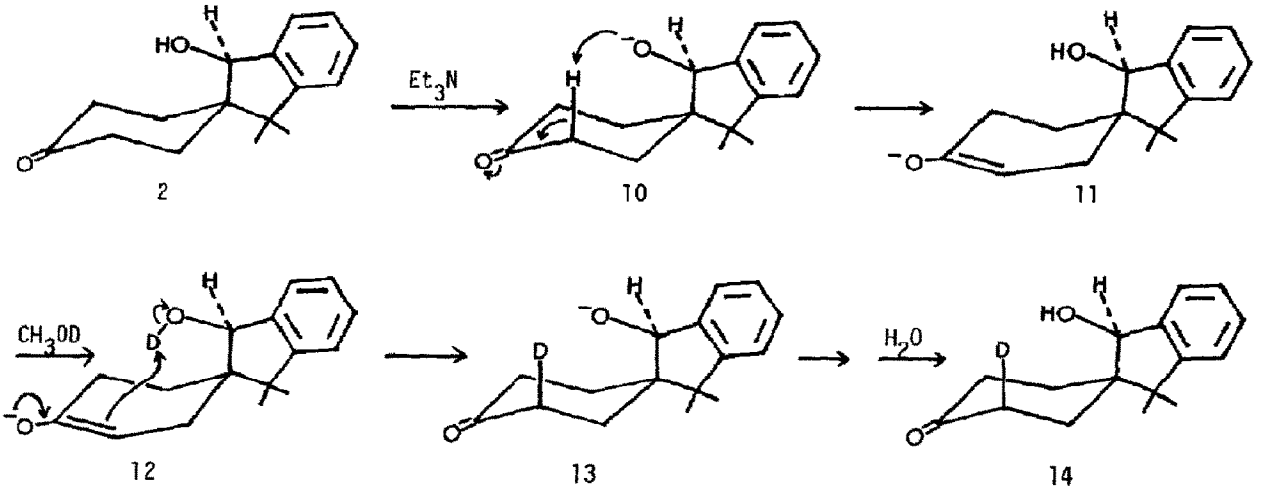


Figure 1. NMR spectrum of 2 in $CDCl_3$ with 0.16 molar ratio of Eu$(fod)_3$

values[6] (ΔEu) were also calculated from the shifted spectra and are likewise recorded in Table 1. Note that the 3[axial] and 5[axial] protons may be distinguished from one another since the former should have its unshifted resonance at lower field and also should possess a ΔEu of higher magnitude, in both cases due to its proximity to the OH group.[6,7] A spectrum of 2 in $CDCl_3$ containing 0.16 mole ratio of $Eu(fod)_3$ presents the 3[axial] proton as a symmetrical triplet of doublets centered at δ 5.20 and nearly free of overlap with adjacent resonances (Fig. 1). In the spectrum of the above deuteration product, measured under identical conditions, this multiplet is reduced to 0.2H intensity; the major deuteration product is, therefore, assigned the 3[axial] structure 14. We suggest[8] that the formation of 14 occurs <u>via</u> the oxanion 10 which acts as an internal base, removing the nearby[9] 3[axial] proton to give the enolate anion 11. Rapid exchange of the hydroxyl proton with the deuterated solvent leads to 12 which, by intramolecular deuteration of the enolate anion, gives 13 and then 14. Note that 12 → 13 is the microscopic reverse of 10 → 11 except for the D in place of H. Thus, the configuration of the deuterium substituent in 14 should be identical with that of the hydrogen removed from 2. This seems to be the first case in which intramolecular catalysis of enolization results in stereochemical selectivity.



Parallel deuteration studies conducted with the bis-nor keto-alcohol 9[10] revealed no special effects attributable to the hydroxyl substituent. This result is not surprising since the stable conformation of 9 is presumably not analogous to 2 but is the alternative chair form in which the OH is far removed from the α-methylene hydrogens.

REFERENCES AND NOTES

1. E. Bergmann, H. Taubadel, and H. Weiss, Ber. 64, 1493 (1931).
2. All new compounds gave spectral and combustion analysis data in agreement with the proposed structures.
3. A. P. Krapcho and A. J. Lovey, Tetrahedron Lett. 957 (1973).
4. All workups included a water wash which replaced hydroxyl deuterium.
5. A complete presentation and discussion of the kinetic data will be published separately by M. L. Miles.
6. P. V. Demarco, T. K. Elzey, R. B. Lewis, and E. Wenkert, J. Am. Chem. Soc., 92, 5734 (1970).
7. N. S. Bhacca and D. H. Williams, "Application of NMR spectroscopy in Organic Chemistry, Holden-Day, Inc., 1964, Chapters 2 and 8.
8. Other possible mechanisms may be formulated which are not excluded by our data.
9. An X-ray crystal study of 2 revealed that, at least in the solid state, the cyclohexanone ring is not appreciably distorted from the expected chair form and that the interatomic distance between the hydroxyl oxygen and the 3[axial]-hydrogen is 2.6 Å. The sum of the van der Waals radii for these two atoms is also 2.6 Å. We are indebted to Mr. Glenn L. Hennessee and Professor Jon Bordner for the X-ray crystallographic study.
10. The synthesis of hydroxy-ketone 9, m.p. 65-67°, was accomplished in 46% overall yield from 1-indanone by a sequence analogous to that employed for 2. A completely different synthesis of 9 (obtained as a gum in 15% overall yield from 4-carbomethoxycyclohexanone) has been recorded.[11]
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