

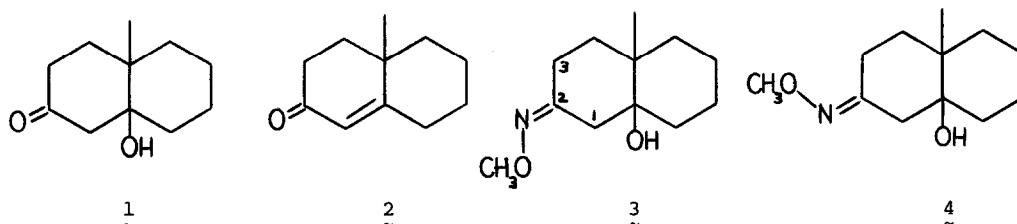
REGIOSELECTIVITY IN α PROTON ABSTRACTION FROM KETONE METHOXIMES

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In our previous studies¹ of nucleophilic amine catalysis of the conversion of β -ketol 1 to enone 2, we did not use an amine of the type which displays the " α effect,"² such as methoxylamine. Not surprisingly, treatment of 1 with methoxylamine produces no 2, but affords instead a 1:1 mixture of stable methoxime isomers 3 and 4.³ These methoximes are quite resistant to base catalyzed dehydration, being only partially converted to methoxime derivatives of 2³ upon treatment with 1 M NaOH in 1:1 H₂O:EtOH at 70° for 24 hr. This reaction can be estimated to be at least 10⁵ slower than hydroxide ion catalyzed dehydration of 1, which has $t_{1/2} \cong 1$ min at pH = 14 at 25°.⁴ It was also discovered that 3 reacts more rapidly than 4 in this dehydration reaction. Since α proton abstraction is presumably involved in the slow step in the dehydration, this observation suggests that 3 is more readily deprotonated at C1 than is 4.



If such apparent regioselectivity in α proton abstraction from methoximes could be confirmed, it would not only clarify the behavior of 3 vs. 4, but might also help to explain the observed preference for heterocyclization syn to the original site of the oxygen atom in the conversion of oximes and their O-alkyl derivatives to aziridines by complex metal hydrides or Grignard reagents.^{5,6} Accordingly, we decided to study the reaction with base of the methoxime of a simple symmetrical ketone. Dibenzyl ketone methoxime (5)⁷ seemed ideally suited for detection of isotopic exchange of α protons. The simple nmr spectrum of 5

(in PhH-D₆) (Figure 1) has the three-proton methoxyl group signal conveniently located at δ 3.94 ppm to serve as an integration standard for the two methylene group signals at δ 3.56 and 3.39 ppm. The latter peaks can be reliably assigned respectively to the α protons syn and anti to the methoxyl group on the basis of a study of methoxime nmr spectra by Karabatsos and Hsi.⁸

Treatment of an ether solution of **5** with 1 equiv of lithium isopropylcyclohexylamide (LICA)⁹ at 25° or 0°, followed by a D₂O workup, afforded material which showed no methoxyl group nmr signal. Under these conditions, α deprotonation was probably being followed by nitrene formation, as in the chemistry referred to earlier.^{5,6}

When the experiment was run at -60°, however, some **5** could be recovered after workup. The product obtained after 2 hr at -60°, followed by addition of CH₃OD, showed clearly, despite the presence of decomposition products, that the peak at δ 3.56 ppm was diminished relative to those at δ 3.94 and 3.39 ppm. Maximum exchange was observed after 8 hr, and prep tlc of the product from this experiment afforded 35% of **5** which had the nmr spectrum (PhH-D₆) shown in Figure 2. The areas of the methoxyl and the anti α methylene proton peaks are still at a 3:2 ratio, but the syn α methylene proton signal area is reduced by ~38%, indicating loss of ~75% of a proton selectively at that site. Part of the remaining signal near 3.56 ppm is broadened and shifted slightly upfield as expected upon introduction of deuterium.¹⁰ Attempts to achieve exchange of more nearly 1.0 proton using longer reaction times and/or excess LICA were unsuccessful.

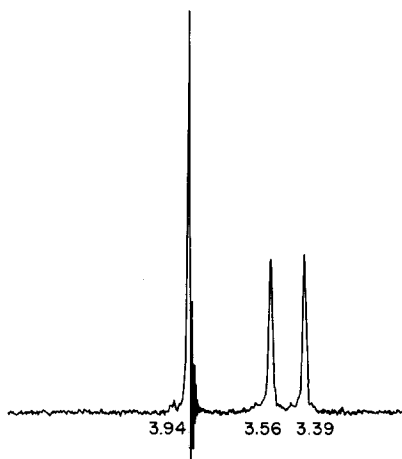
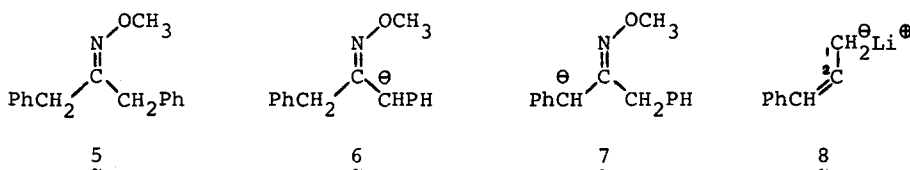


Figure 1. Partial ¹H Nmr Spectrum of **5**.



Figure 2. Partial ¹H Nmr Spectrum of **5** after Treatment at -60° with:
1) LICA (8 hr); 2) CH₃OD.

Since it seems safe to assume that reaction of the anion from **5** with CH_3OD will be rapid and irreversible, the result shown in Figure 2 establishes the structure of that anion as at least 95% **6**, with no more than a few per cent of **7** present. This does not necessarily prove that the proton abstraction process was regioselective, because it is impossible to rule out isomerization between **6** and **7**, even at -60° . Methoximes themselves are very resistant to thermal isomerization¹¹, but the anion should have a much lower barrier to rotation. Phenylallyl lithium (**8**) has ΔG^\ddagger for $\text{C}_1\text{-C}_2$ rotation in ether at -60° of roughly 17 kcal/mole¹², and the canonical form of **6** or **7** corresponding to **8** should be a significant contributor to the structure of the anion from **5**. If the thermal interconversion **6** \rightleftharpoons **7** has $\Delta G^\ddagger < 15$ kcal/mole, such a process could be significant on the time scale of our deprotonation experiment.



It is reasonable to argue, however, that the transition state leading to the highly unstable anion from **5** will partake of any factors which make **6** more stable than **7**. On the basis of this Hammond postulate argument,¹³ it can be claimed that **6** is the kinetic product in α deprotonation, irrespective of whether **6** \rightleftharpoons **7** occurs at -60° . The greater reactivity of **3** than **4** in base catalyzed dehydration also supports the view that the α proton abstraction itself is regioselective.

An explanation for this regioselectivity in α deprotonation of methoximes by base can be offered¹⁴ on the basis of the electronic structures of the derived anions (and therefore of the transition states leading to them). In a syn α anion like **6**, but not in **7**, there is a six π electron system with a configuration which permits an attractive nonbonded interaction between the α carbon and the oxygen. Such stabilizing interaction has been predicted by Epiotis,¹⁵ whose molecular orbital calculations on cis-1,2-difluoroethylene gave results consistent with the experimental evidence¹⁶ that it is more stable than trans-1,2-difluoroethylene. The present results unfortunately do not permit any more than a rough estimate of a minimum energy value of around 1.5 kcal/mole for this stabilization in the case of **6**, because the nmr method employed does not exclude the possibility that there is a small amount of a minor isomer present.

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