REINVESTIGATION OF THE REGIOSELECTIVITY OF DEPROTONATION OF
KETONE DIMETHYLHYDRAZONES

Michael E. Jung[*1] and Teresa J. Shaw

Department of Chemistry, University of California, Los Angeles, CA. 90024

Robert R. Fraser,[*] Jacques Banville and Kevser Taymaz

Department of Chemistry, University of Ottawa, Ottawa K1N 9B4 Canada

Abstract: The lack of regioselectivity in the deprotonation of ketone dimethylhydrazones by lithium diethylamide has been determined by ^{13}C NMR spectroscopy of deuterium labelled samples.
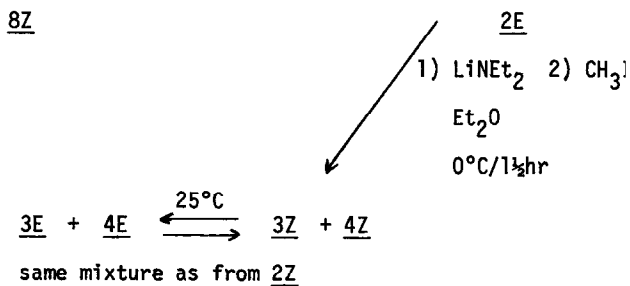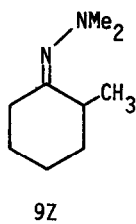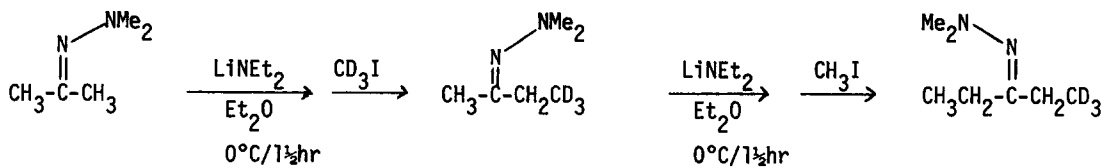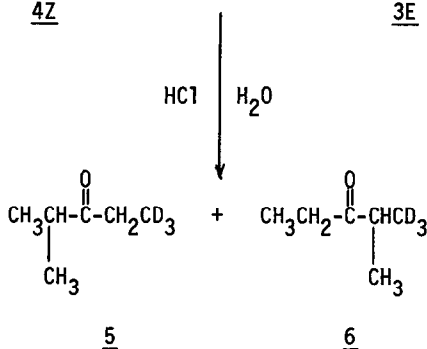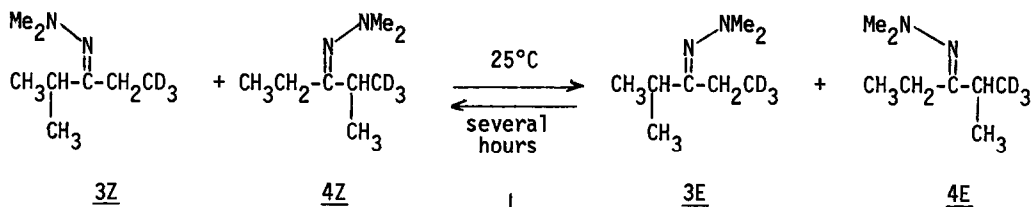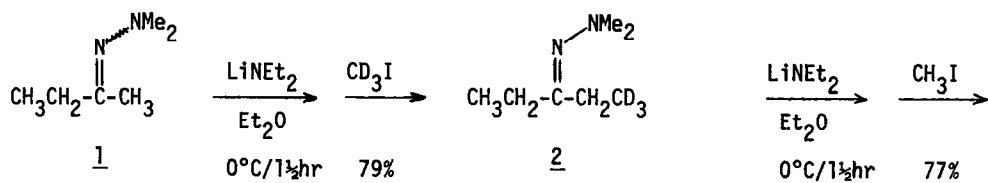
While studying the syn-alkylation of dimethylhydrazones of ketones, we[2] obtained preliminary evidence indicating a kinetic preference for anti deprotonation in symmetrically substituted ketone dimethylhydrazones. Subsequently, separate reports of preferred syn deprotonation in two similar systems, oxime dianions[3] and oxime ether anions[4] appeared indicating kinetic preference for proton abstraction to parallel the thermodynamic anion stability preference in those systems.[5] In addition, the thermodynamic preference for the syn anion of hydrazones[5,6,7] has received substantiative spectral evidence,[6] all of which has prompted us to reinvestigate the original reaction sequence. Since the original structural assignments were based on ^1H NMR spectroscopy,[8] we have utilized ^{13}C NMR spectroscopy as the primary analytical tool for structure redetermination.[9] We now report the results of these experiments which indicate clearly that the original structure determination was incorrect and that the experiments cannot provide any evidence regarding the stereochemistry of the deprotonation step. We have demonstrated separately that ketone dimethylhydrazones are configurationally unstable in the presence of base and that it is this property which precludes the obtaining of evidence regarding the stereochemistry of the deprotonation step.

Deprotonation of the dimethylhydrazone of 2-butanone 1 as a mixture of geometric isomers with lithium diethylamide in diethyl ether at 0 °C followed by treatment with trideuteromethyl iodide afforded the Z-isomer of the deuterated 3-pentanone dimethylhydrazone 2Z as shown. A second sequence of deprotonation followed by methylation with methyl iodide converted 2Z into a

mixture of the alkylation products 3Z and 4Z. These were then allowed to warm to 25 °C for several hours to ensure complete equilibration of hydrazone isomers. Direct ^{13}C NMR analysis of the equilibrated mixture of the dimethylhydrazone products 3 and 4 allowed one to easily determine the relative ratio of all of the four components by simple integration. A trideutero-methyl group attached to a methine or methylene carbon causes an upfield shift of the undeuterated carbon of approximately 0.2 ppm.[10] Thus the ^{13}C NMR spectrum of the mixture exhibited the following absorptions: methine carbons: 3Z, 24.2 ppm; 4Z, 23.9 ppm; 3E, 34.6 ppm; 4E, 34.4 ppm; methylene carbons: 3Z, 28.6 ppm; 4Z, 28.8 ppm; 3E, 21.8 ppm; 4E, 22.0 ppm. Integration of the pertinent peaks[11] indicated a mixture of 3Z;4Z;3E;4E of 15:15:35:35, respectively, corresponding to an essentially 1:1 mixture of 3 and 4. In order to check the validity of this analysis, the mixture of alkylated dimethylhydrazones, 3 and 4, was hydrolyzed under acidic conditions to give a mixture of the ketones, 5 and 6 respectively. ^{13}C NMR analysis of this ketone mixture indicated two sets of absorptions for the methine and methylene carbons assigned as follows: methine: 5, 40.6 ppm; 6, 40.4 ppm; methylene: 5, 33.2 ppm, 6, 33.4. The integration of these absorptions showed that the mixture was approximately 1:1.[11]

The observation of equal amounts of alkylation products 3 and 4 suggested the possibility that equilibration of the label in 2 was occurring prior to the alkylation step. To verify this interpretation, the isomeric deuterated 3-pentanone dimethylhydrazone, 2E, was methylated. This compound was prepared by alkylation of acetone dimethylhydrazone with trideuteromethyl iodide to give 8Z which on further methylation gave 2E. Using the same conditions as for 2Z, methylation of 2E afforded the same mixture of alkylated hydrazones 3 and 4 as obtained from 2Z. Obviously the stereochemical disposition of label in 2 has been lost prior to alkylation, presumably by a base-catalyzed process.

Previously, it was demonstrated that acetone dimethylhydrazone underwent "inversion" at nitrogen via a process having a markedly solvent-dependent rate.[12] Detailed investigation established that the inversion proceeded via acid-catalyzed formation of an enehydrazine tautomer. The effect of base catalysis was not investigated. To demonstrate the susceptibility of a hydrazone to base-catalyzed inversion, we have measured the rate constants for the isomerization of syn-2-methylcyclohexanone DMH, 9Z,[13] to its equilibrium distribution of isomers. Isomerization of 9Z in benzene containing 0.001 M piperidine occurred with a half-life of two minutes at 34 °C (k_2 = 5 ℓ m^{-1}s^{-1}). Clearly, the isomerization of the hydrazone by base is a very facile process.[14]

$$CH_3CH_2-C-CH_3 \xrightarrow[\text{Et}_2O]{\text{LiNEt}_2} \xrightarrow[79\%]{CD_3I} CH_3CH_2-C-CH_2CD_3 \xrightarrow[\text{Et}_2O]{\text{LiNEt}_2} \xrightarrow[77\%]{CH_3I}$$

1   0°C/1½hr   79%   **2**   0°C/1½hr   77%

3Z   **4Z**   25°C several hours   **3E**   **4E**

HCl | H₂O

5   **6**

7   LiNEt₂ / Et₂O / 0°C/1½hr   CD₃I   **8Z**   LiNEt₂ / Et₂O / 0°C/1½hr   CH₃I   **2E**

1) LiNEt₂ 2) CH₃I

Et₂O

0°C/1½hr

9Z

3E + 4E ⇌ 3Z + 4Z (25°C)

same mixture as from **2Z**

Presumably, then, in THF, in the presence of the very strong $LiN(Et)_2$, $\underline{2Z}$ and $\underline{2E}$ equilibrate rapidly.

In summary, the ease of inversion at the nitrogen of ketone DMH's via base-catalysis prevents the determination of the stereochemistry of the deprotonation step. Nevertheless, in the absence of definitive information, it is most probable that, as found for oximes and oxime ethers, $\underline{syn}$ deprotonation occurs faster than $\underline{anti}$ deprotonation.

<div align="center">REFERENCES AND NOTES</div>

1. Camille and Henry Drefus Teacher - Scholar, 1978-1983, and Fellow of the Alfred P. Sloan Foundation, 1979-1981.

2. M. E. Jung and T. J. Shaw, Tetrahedron Lett., 3305 (1977).

3. R. E. Lyle, H. M. Fribush, G. G. Lyle, and J. E. Saavedra, J. Org. Chem., 43, 1275 (1978).

4. H. E. Ensley and R. Lohr, Tetrahedron Lett., 1415 (1978).

5. R. R. Fraser and K. L. Dhawan, Chem. Commun., 674 (1976). M. E. Jung, P. A. Blair and J. A. Lowe, Tetrahedron Lett., 1439 (1976). T. A. Spencer and C. W. Leong, Tetrahedron Lett., 3889 (1975).

6. M. Newcomb and D. E. Bergbreiter, Chem. Commun., 486 (1977).

7. E. J. Corey and D. Enders, Chem. Ber., 111, 1337 (1978).

8. The unfortunate overlap of methyl absorptions gave an apparently simple set of peaks, leading to the erroneous conclusion as demonstrated herein.

9. (a) R. R. Fraser, K. L. Dhawan and K.Taymaz, Org. Mag. Reson., 11, 269 (1978); (b) H. Ahlbrecht, E. O. Düber, D. Enders, H. Eichenauer and P. Weuster, Tetrahedron Lett., 3691 (1978); (c) P. Geneste, R. Durand, J. M. Karmenka, H. Beierbeck, R. Martino and J. K. Saunders, Can. J. Chem., 56, 1940 (1978).

10. J. B. Stothers, C. T. Tan, A. Nickon, F. Huang, R. Sridhar and R. Wiglein, J. Am. Chem. Soc., 94, 8581 (1972).

11. The ratio of isomers is estimated to be accurate to ± 5%, i.e., 50 ± 5% of each isomer, since the isotopic shift does not separate the signals completely. The introduction of deuterium will not influence the integral intensity as relaxation by the protons directly bonded to carbon will dominate.

12. H. O. Kalinowski, H. Kessler, D. Liebfritz and A. Pfeffer, Chem. Ber., 106, 1023 (1973); see also C. I. Stassinopoulou, C. Ziodrou and G. J. Karabatsos, Tetrahedron, 32, 1147 (1976).

13. This compound, described elsewhere[7] as an 83:17 mixture (E:Z) can be obtained in pure Z form[2] by careful work-up (temperature < 25°) and avoidance of halogenated solvents.

14. Whether inversion occurs via the anion or via the enehydrazine tautomer is not known.