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A RE-INTERPRETATION OF THE NMR SPECTRA OF SOME 1-ALKYL-1,2,3,4-TETRAHYDRO-2-OXO-3-AZOCINE CARBOXYLIC ACID DERIVATIVES

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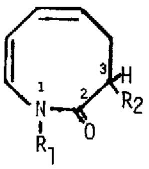
Summary: It is shown that the title compound, as well as related compounds, give temperature dependent chemical shifts owing to population changes between rapidly equilibrating rotamers, and not as a result of dynamic NMR effects.

Somekawa et al.[1] have recently observed "extraordinary splitting patterns" in the ^1H NMR of the N-alkyl group (ethyl, isopropyl, isobutyl, but not methyl) in various tetrahydro-2-oxo-3-azocine derivatives (I to IV) and related compounds. In I, II, and IV the N-CH_2 resonances have two quite different chemical shifts which persist to 200°C, and the authors deduce that $\Delta G^{\ddagger}$ (presumably for a process which exchanges the environment of the CH_2 protons) is greater than about 23 kcal/mol. Although this deduction is quite correct, the authors[1] do not seem to appreciate that an exchange of the chemical shifts of the diastereotopic[2] CH_2 protons of an N-alkyl group in these compounds requires an inversion of configuration at C-3, which is a chiral center (asymmetric carbon), in addition to a conformational process (a ring inversion, which changes the chirality of the ring system). Inversion at C-3 will not take place unless some bond to that atom is broken, and is therefore not expected to be occurring under the conditions used.[3]



I: $R_1 = CH_2CH_3$; R_2 = CN
II: $R_1 = CH_2CH_3$; $R_2 = CO_2CH_3$
III: $R_1 = CH(CH_3)_3$; $R_2 = CO_2CH_3$
IV: $R_1 = CH_2\text{-}CH(CH_3)_3$; $R_2 = CO_2CH_3$
V: $R_1 = CH_2CH_3$; R_2 = H

Furthermore, the authors do not distinguish between two completely different phenomena: (1) a true dynamic NMR effect, where line broadening, followed by coalescence and line resharpening, takes place, and (2) a mere merging of lines resulting from temperature dependent chemical shifts, and taking place without any line broadening or resharpening. The latter effect undoubtedly explains the "coalescence" of the methyl resonances in the N-isopropyl group in III at near 140°C. The claimed $\Delta G^{\ddagger}$ of 21.6 kcal/mol is thus meaningless. Furthermore, in IV($R_1 = CH_2\text{-}CH(CH_3)_3$, it is claimed that $\Delta G^{\ddagger}$ for the CH_3 groups is 19 kcal/mol, whereas for the methylene group $\Delta G^{\ddagger}$ is > 22.8

kcal/mol. The sudden apparent appearance of two separate processes is not explained by the authors. In fact, the behavior of the isobutyl compound is excellent evidence that the new interpretation given above for the isopropyl compound is correct.

The interpretations given above also undoubtedly hold for compounds labelled 2, 3, and 4 in the original paper.[1] Finally, Somekawa et al. have made the key observation that V, which lacks the crucial chiral center at C-3, gives a clean quarter for the N-α methylene protons. Thus, ring inversion in V is fast at room temperature, as expected,[4] and takes place between two iso-energetic mirror-image conformations. The N-α methylene protons in V are therefore not diastereotopic at room temperature.

There is nothing unusual in the (large) temperature dependence of the chemical shifts of the N-alkyl substituents in compounds, such as I, which have an asymmetric carbon, and which have the possibility of existing in more than one conformation or rotameric form.[5] In a solution of I (and related compounds) the ring is probably largely in the conformation found in crystalline I, where the cyano group is exo, but the ethyl group should exist as more than one rotamer about the N-CH_2 bond, unlike the situation in the crystal. Since the two (or perhaps three) rotamers are different, they will have different energies and be differently populated at different temperatures. As pointed out by Somekawa et al. the environment of the N-CH_2 protons consists of groups which are highly magnetically anisotropic. Thus the two N-CH_2 chemical shifts will be sensitive (and different) functions of the populations of the rotamers, as observed.

REFERENCES AND NOTES

(1) K. Somekawa, S. Kumamoto, T. Matsuo, and I. Ueda, Tetrahedron, **36**, 81 (1980).

(2) M. Raban and K. Mislow, Top. Stereochem., **1**, 1 (1967).

(3) Since the C-3 anion is resonance stabilized, base catalysis of C-3 enantiomerization is a possibility in the presence of a sufficiently strong base, but is highly unlikely in trichlorobenzene solutions of the neutral azocine derivatives.[1]

(4) Conformational processes in 1,3,5-cycloheptatriene are very fast above -100°C, F. A. L. Anet, I. Yavari, Tetrahedron Letters, 4221 (1975).

(5) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed., Pergamon Press, Oxford, 1969, chapter 5.2.

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