Intrinsic Diastereotopism of Geminal Protons in Quaternary Salts from Quinuclidine and Hexamine

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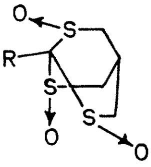
Summary Intrinsic diastereotopism has been demonstrated directly by room-temperature n.m.r. spectroscopy for the geminal ring-methylene protons adjacent to positive nitrogen in quaternary salts derived from quinuclidine or hexamine and suitable chiral alkylating agents (α-phenylethyl bromide and ethyl α-bromopropionate).

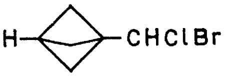
IN compounds $A\cdot BC_2\cdot D_n\cdot E$ or $A\cdot BC_2\cdot E$ where E is a chiral group the geminal atoms or groups C are diastereotopic and therefore anisochronous.[1] In most examples this is partly because of preferred rotameric orientations about the E–D or E–B bonds and only partly because of an intrinsic effect[1–3] which would persist even if all three rotamers were equally populated. For certain types of molecule[1,2] the conformational-bias effect is eliminated by symmetry, and the intrinsic effect may in principle be shown directly. So far there has been only one such experimental demonstration,[2] with the propeller-type molecules (I), where the hydrogen or fluorine nuclei in geminal methyl ($R = CMe_2$-OH) or trifluoromethyl [$R = C(CF_3)_2OH$] groups were shown to have different chemical shifts. The hypothetical molecule (II) might also be suitable[1] for demonstration of intrinsic diastereotopism for the ring-methylene protons. The relevant stereochemical features of (II) also exist in a few synthetically more accessible compounds, an examination of which led to our results.

In the 100 MHz spectrum of a solution of the quaternary salt (III; R = PhCHMe) in $(CD_3)_2SO$ the six ring-methylene protons adjacent to positive nitrogen and the remaining six appear as complex multiplets at lower and higher field respectively. Irradiation at τ 8·12 in the higher-field multiplet resulted in transformation of the other into an AB quartet,† with H_A, H_B at τ 6·42, 6·515 and J_{AB} 12·5 Hz. Separation of the H_A, H_B signals was less marked in a similar experiment with solutions in CD_3OD, only a broad singlet being obtained on decoupling of the adjacent upfield protons. An AB quartet (H_A, H_B at τ 6·26, 6·35, J_{AB} 12·5 Hz) was also obtained with a solution of the salt (III; $R = MeCH\cdot CO_2Et$) in $(CD_3)_2SO$ on irradiation at τ 8·06; a similar result was achieved in CD_3OD, but not in $CDCl_3$. With the salt (III; R = Me) only a singlet was obtained for the downfield ring-methylene protons on appropriate decoupling.

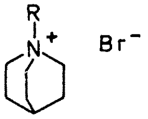
We could not obtain a satisfactory derivative of hexamine with ethyl α-bromopropionate, but the n.m.r. spectrum of the salt (IV; R = PhCHMe) in $(CD_3)_2SO$ had an AB quartet (H_A, H_B at τ 4·77, 4·98, J_{AB} 12 Hz) for the six ring-methylene protons adjacent to positive nitrogen. The other six unexpectedly appeared as a sharp singlet at τ 5·47 apparently due to a cancellation of effects (*e.g.*, the field-effect of the positive pole and the benzene-ring anisotropy); this was also observed in spectra of the salt (IV; $R = PhCH_2$) in CD_3OD or $(CD_3)_2SO$ (two six-proton singlets) but not in that of (IV; R = Me and I^- for Br^-) where in $(CD_3)_2SO$ the lower-field ring methylene protons appeared as a singlet at τ 4·75 and those at higher field as an AB quartet (H_A, H_B at τ 5·29, 5·45, J_{AB} 12 Hz).



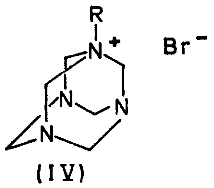
(I)



(II)



(III)



(IV)

Since in any salt (III or IV) examined the three rotamers interconvertible by rotation of R about the N^+–R bond are of equal stability because of the symmetry of the quinuclidine or hexamine moieties, the observed diastereotopy of the ring-methylene protons (two groups of three protons each, type H_A, H_B) adjacent to positive nitrogen when R is chiral must be "intrinsic"[1–3] in character. However, neither in these examples nor in those of ref. 2 can the observed chemical-shift differences be said not to depend in *any* way on preferred conformation. The δ_{AB} values depend on preferences *within* the R groups in compounds (I; III, IV), *e.g.* on the orientation of OH in the propeller-type molecules, or of Ph and CO_2Et in the others. Groups R with only axially symmetric sub-units (*e.g.*, Me, C≡N, Br) would be less synthetically convenient, and the value of using them is doubtful. Solvent effects on the chemical shifts are marked, and the symmetries of solvation shells cannot be readily controlled.

We have not been able to demonstrate chemical-shift differences between geminal groups in the ^1H n.m.r. spectra of compounds containing $-\overset{+}{N}(CH_3)_2CD_3$ or $-CH_2D$ in a variety of chiral environments.

(*Received, April 9th,* 1970; *Com.* 498.)

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† Actually three identical superimposed AB quartets, one for each methylene group. To avoid more cumbersome descriptions, the same meaning is also intended elsewhere in the text where six protons (3 × 2) are described as forming an "AB quartet."

[1] For nomenclature see K. Mislow and M. Raban, *Topics Stereochem.*, 1967, **1**, 1.

[2] G. Binsch and G. R. Franzen, *J. Amer. Chem. Soc.*, 1969, **91**, 3999.

[3] H. S. Gutowsky, *J. Chem. Phys.*, 1962, **37**, 2196.