Magnetic Nonequivalence of an Isopropyl Group due to Steric Hindrance

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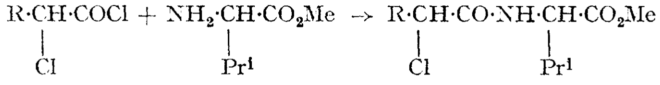
MAGNETIC NONEQUIVALENCE of an isopropyl group in asymmetrical compounds is generally attributed to a preferred conformation effect caused by solvent,[1] phenyl substitution,[2] hydrogen bonding,[3] or a combination of these factors.[4,5] However, direct evidence for a purely steric contribution is lacking, although this possibility has been discussed briefly in previous work.[6]

In connection with our current interest concerning steric effects on physical properties,[7] a series of

L-α-chloroacyl chlorides (Ia—d)[8] were treated with L-valine methyl ester (II) to yield the corresponding L-α-chloroacyl-L-valine methyl esters (IIIa—d).[9] A solution of L-α-chloropropionyl-L-valine methyl ester (IIIa) in deuterochloroform with tetramethylsilane as an internal standard at 60 Mc./sec. gave an n.m.r. spectrum that contained signals for the amide hydrogen (7·16 δ, broad doublet), the valyl and chloromethine hydrogens (4·54 and 4·20 δ, overlapping quartet, *J* 6·5 c./sec. and pair of doublets, *J* 9·0 and 5·0 c./sec.), the ester methyl (3·75 δ, singlet), the isopropyl methine hydrogen (2·17 δ, sextet), the chloropropionyl methyl (1·72 δ, doublet, *J* 6·5 c./sec.) and the valyl-methyls (0·97 and 0·93 δ, quartet, *J* 6·5 c./sec.). The doubled doublet for the isopropyl group is slightly unsymmetrical with a chemical shift difference of about 2·0 c./sec. The corresponding spectrum for L-α-chloro-4-methylpentanoyl-L-valine methyl ester (IIIb) is simpler; the somewhat larger chemical-shift difference for the valyl-isopropyl (0·96 δ, doublet) is partially masked by the α-chloroacyl-isopropyl (1·00 δ, doublet). The L-α-chloro-3-methylbutanoyl-L-valine methyl ester (IIIc) spectrum is more complex, but a series of signals can be assigned to the α-chloroisopropyl (1·06 and 0·95 δ, pair of doublets, *J* 6·5 c./sec.) and valyl-isopropyl (0·97 and 0·92 δ, pair of doublets, *J* 6·5 c./sec.) substituents. The shift is about 4·0 c./sec. and continues the trend towards an increasing separation. Finally, the spectrum of L-α-chloro-3,3-dimethylbutanoyl-L-valine methyl ester (IIId) exhibits the expected α-chloro-t-butyl peak (1·15 δ, singlet), as well as the usual valyl-isopropyl group (0·97 and 0·88 δ, pair of doublets, *J* 6·5 c./sec.). The chemical shift here amounts to 7·0 c./sec.



$$\underset{\text{Cl}}{\text{R}\cdot\text{CH}}\cdot\text{COCl} + \text{NH}_2\cdot\underset{\text{Pr}^{\text{i}}}{\text{CH}}\cdot\text{CO}_2\text{Me} \rightarrow \underset{\text{Cl}}{\text{R}\cdot\text{CH}}\cdot\text{CO}\cdot\text{NH}\cdot\underset{\text{Pr}^{\text{i}}}{\text{CH}}\cdot\text{CO}_2\text{Me}$$

(I) (II) (III)

a; R = Me
b; R = Bu^{i}
c; R = Pr^{i}
d; R = Bu^{t}

The gradual increase in separation of the valyl-isopropyl signal is indicative of the operation of an additive steric factor, particularly with respect to a preferred configuration for the substituents at the α-asymmetrical carbon. An application of the "rule of six" to the α-chloroacyl moiety of these compounds (IIIa—d) gives six numbers of 0, 3, 6, and 9, respectively.[10] This suggestion has been used earlier to rationalize hydrolysis rates of di- and poly-peptides,[11] as well as the separation of diastereoisomeric peptide[7] and ester pairs[12] on gas chromatography. Interestingly, a similar explanation has been mentioned in an investigation on the extent of magnetic nonequivalence found in various isopropyl 1-phenylethyl ethers.[13] The n.m.r. spectra of the L-α-chloroacyl-D-valine methyl ester series[9] were identical with those of the L–L compounds discussed here.

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