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STRUCTURAL ASSIGNMENTS OF 1-AMINO-2-PHENYLCYCLOHEXANE-CARBOXYLIC ACIDS BY PROTON NMR CHEMICAL SHIFTS

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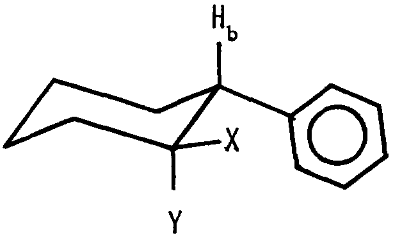
We report here the structural assignments of conformationally-restricted cyclic analogues of β-phenylalanine, 1 and 2, obtained from 2-phenylcyclohexanone by the Bucherer Method[1,2] and the Strecker Method[3,4], respectively. The structural assignment of cyclic amino acids synthesized via these routes has been controversial, and contradictory assignments have appeared in the literature[5,6,7]. In this communication we show how measurement of the chemical shifts of simple esters and amides of 1 and 2 leads to unequivocal geometric isomer assignments.

We prepared O-methyl and N-acetyl derivatives of 1 and 2 (9-12) and of model carboxylic acids and amines (3-8). Both the configurational[8,9] and conformational[10] assignments of the model compounds are well established. The variation in the chemical shift of the benzylic proton NMR bands (δ_{H_b}) of compounds 3-12 reflects the shielding/deshielding properties of the substituents at C_1 (X and Y in the formula shown). By measuring δ_{H_b} for the model derivatives (3-8) and derivatives of 1 and 2 (9-12), we have factored empirically (by inspection) the incremental contribution for each substituent (Table I). These incremental values show near-ideal additivity for this series of compounds, and the close agreement between calculated and observed chemical shifts leaves no doubt as to the structural assignments of 1 and 2. We anticipate that this approach will prove applicable to other similar sets of conformationally-restricted compounds.



1 X= NH_3^+, Y= COO^-

2 X= COO^-, Y= NH_3^+

Table I. Calculated and Observed δ_{H_b}'s (ppm) at 60MHz in DMSO-d_6[a]

compound	X=	Y=	δH_b(calculated)	δH_b(observed)
3	-NHCOCH$_3$(+.20)	-H (-.10)	2.45	2.48
4	-H (-.20)	-NHCOCH$_3$(+.60)	2.75	2.77
5	-H (-.20)	-COOH (+.45)	2.60	$\sim$2.55[b]
6	-H (-.20)	-COOCH$_3$ (+.20)	2.35	$\sim$2.37[b]
7	-COOH (+.45)	-H (-.10)	2.70	$\sim$2.64[b]
8	-COOCH$_3$ (+.20)	-H (-.10)	2.45	$\sim$2.49[b]
9	-NHCOCH$_3$(+.20)	-COOH (+.45)	3.00	2.98
10	-NHCOCH$_3$(+.20)	-COOCH$_3$ (+.20)	2.75	2.77
11	-COOH (+.45)	-NHCOCH$_3$(+.60)	3.40	3.43
12	-COOCH$_3$ (+.20)	-NHCOCH$_3$(+.60)	3.15	3.09

[a] δ_{H_b}'s(calculated) are obtained by summing the base value (2.35 ppm) and the parenthetical increments for X (the equatorial substituent) and Y (the axial substituent). δ_{H_b}'s(observed) are measured in 10% w/v solutions, relative to TMS.

[b] The signal for H_b overlaps that from H_1 (X or Y in the formula shown), resulting in approximately ±0.08ppm maximum uncertainty in the measured chemical shifts.

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