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CONFIGURATIONAL ANALYSIS OF SOME DECALIN AMINO-ACIDS: NOVEL CRITERIA BASED ON pK CHANGES IN BINARY AQUEOUS SOLVENTS

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Munday[1] has assigned the configurations of certain alkyl-substituted 1-aminocyclohexane-1-carboxylic acids on the basis, in part, of their pK values. It has previously been argued[2] that the greater solvation possible in the equatorial position should make equatorial acids or bases stronger than their axial epimers. In attempting to use this argument in the configurational analysis of certain cis- and trans- aminodecalin carboxylic acids, we have been forced to challenge these criteria and to evolve new ones which it is the purpose of this communication to describe.

The six compounds whose pK values are reported in the Table are all too insoluble in water for accurate aqueous pK values to be determined directly, and it was hoped to extrapolate from aqueous acetone by making use of a claim by Laloi-Diard and Rubinstein[3] that, in any binary aqueous solvent mixture, a graph of pK vs. D^{-1} will generally give a linear plot. We do not find this to be so, which is more in accord with other workers' experience[4a], though a considerable improvement in linearity results if D^{-1} is replaced by volume% acetone. Nevertheless, we do not regard any such extrapolation to water as sound, so no estimate of aqueous pK appears in the Table. Even a cursory inspection of the data, however, will reveal that rates of change (Δ pK) vary widely between epimers: it is on this fact that the following argument rests.

TABLE

pK Values of Decalin Amino-Acids

	67% v/v Acetone	50% v/v Acetone	25% v/v Acetone	Δ pK
(1) acidic	3.76	3.49	3.19	0.57
basic	10.33	10.28	10.20	0.13
(2) acidic	3.90	3.52	3.15	0.75
basic	10.07	10.05	10.03	0.04
(3) acidic	3.89	3.60	2.92	0.97
basic	10.19	10.09	10.05	0.14
(4) acidic	3.73	3.40	3.21	0.52
basic	10.27	10.14	9.89	0.38
(5) acidic	3.58	3.35	3.06	0.52
basic	10.36	10.26	10.12	0.24
(6) acidic	[a]	[a]	~2.7	-
basic	10.96	10.37	9.56	1.40

[a] see text

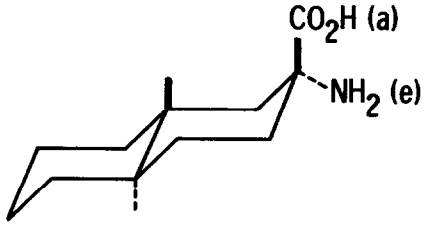
(1) trans-2-aminodecalin-2-carboxylic acid, Bucherer product
(2) trans-2-aminodecalin-2-carboxylic acid, Strecker product
(3) cis-2-aminodecalin-2-carboxylic acid, Bucherer product
(4) cis-2-aminodecalin-2-carboxylic acid, Strecker product
(5) trans-1-aminodecalin-1-carboxylic acid, Bucherer product
(6) cis-1-aminodecalin-1-carboxylic acid, Bucherer product

Munday's configurational analysis[1] is based on the argument[2] that the stronger acid of a pair of epimers will be that in which the carboxyl group possesses the equatorial conformation. This argument should apply equally to the amino-group, yet, in four pairs out of the five that Munday lists, its application would reverse his assignment. Munday notes this dichotomy but remarks[1] that "for the present equilibrium, $^{+}NH_3\text{-}R\text{-}CO_2^{-}$ $\underset{+H^+}{\overset{-H^+}{\rightleftharpoons}}$ $NH_2\text{-}R\text{-}CO_2^{-}$, solvation effects might be less easily interpreted." The point is granted, but it applies equally to either ionisation process.

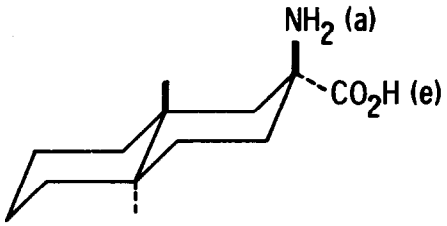
Since induction and hyperconjugation may strengthen or weaken epimeric acids and bases quite independently of differential solvation, and since in any case this latter argument as used previously quite neglects the unionised species. we feel it unsound to base arguments on pK values *per se*, especially when the differences are small. We prefer the following argument. If we suppose that the equatorial position, being less shielded. is more sensitive than the axial to changes in solvation, and that ions being

more solvated are equally more sensitive to changes in solvation than the unionised species, we need make no assumptions as to pK values absolutely. We note that the basic group is more sensitive to solvation changes in (1) than in (2), the acid group in (2) than in (1), and we therefore conclude that $-NH_2$ is equatorial in (1) and -COOH equtorial in (2). Inspection of the data suggests that (1) may well be the stronger base in water, and (2) the stronger acid, but the argument does not require this. Its soundness is based on the postulate that electronic influences should be solvent-independent, at least over the required range, and so should factor out when rates of change are examined. It is proof against the accidental cross-overs that can arise from this source, are clearly visible in the Table, and may have vitiated Munday's conformational analysis[5].

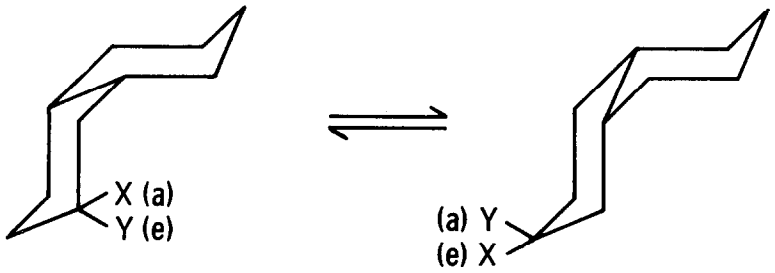
Trans-decalin has a virtually rigid conformation [6,7]; this fact and the above argument fixes the configurations of (1) and (2) as illustrated. Cis-decalin however is much more flexible, and the cis-aminoacids (3) and (4) behave quite differently. Rates of change of pK in binary aqueous solvents commonly become greater as pure water is approached [4a] and in general this is true here, but there are two exceptions. The amino-group of (3), and the carboxylate group of (4), approach constancy of pK in highly aqueous solution. Tentatively, it is suggested that their conformation changes with solvent composition, these two groups going predominantly into the axial position as pure water is approached. Of the two stable conformations for cis-decalin[7], one (A) involves severe 1:3 interaction with whichever 2-substituent takes up the axial position, whereas in the other (B) this is much less. Consequently while conformation (B) should always be somewhat favoured, its relative stability is likely to increase as the solvation shell of the axial substituent enlarges, i.e. as aqueous conditions are approached. It follows that the group Y should be that whose pK approaches constancy in highly aqueous solution, whereas X by contrast should show an abnormally enhanced rate of change. The configurations of (3) and (4) are assigned in this way as illustrated. This argument is additional to that based on ΔpK, which in fact leads to the same conclusion. The configurations of the products derived by Bucherer and Strecker synthesis differ, therefore, in the cis- and trans- cases.



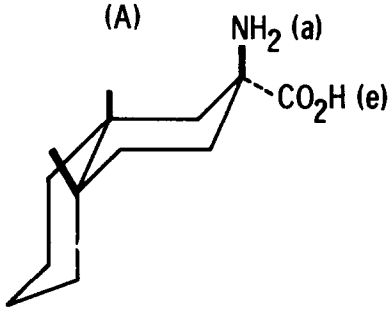
(1)



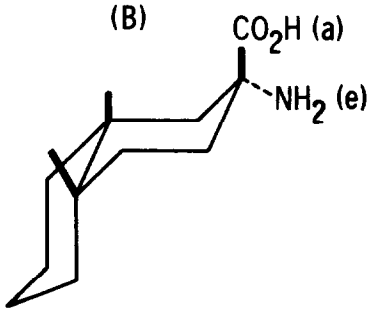
(2)



(A) (B)



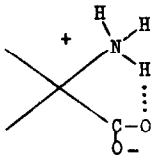
(3)



(4)

Further support for these assignments has been obtained from deamination studies of the decalin amino-acids; their infrared spectra; and the nuclear magnetic resonance spectra of the isomeric spiro-hydantoins.[5]

These criteria cannot be used to assign the conformations of (5) and (6) since their Strecker analogues could not be prepared.[5] It is suggestive that (5) resembles (1), but proof is lacking. The behaviour of (6) is without parallel among these compounds. As an acid it is so strong that only "mirages"[4b] resulted from the attempt to measure its pK value. As a base, its pK varies with solvent to an extent wholly exceptional for an amine. Very tentatively, we suggest that the zwitterion may hydrogen bond in this manner:



The consequence of such bonding would be resistance to removal of a proton, so a rise in pK. Intramolecular hydrogen bonding in solution is expected to be stable only when the bond is shielded or in poorly solvating media. Both criteria are satisfied: the 1-position of cis-decalin is much the most crowded of those considered here, and pK rises sharply as water content falls. Angle compression as a result of crowding would shorten and greatly strengthen such a bond and may also be a major factor. The exceptionally low pK value as aqueous conditions are approached may reflect the increasing dominance of poor solvation. On present evidence, speculation as to conformation is pointless in this case.

Determinations of pK were carried out by potentiometry at 0.01 M on a Metrohm Potentiograph, and dilution corrections[4c] were incorporated. The experimental details, together with other chemical and physical evidence in favour of these assignments, and the other aspects of this work, will be published more fully elsewhere.[5]

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