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CONFORMATIONAL EQUILIBRIA IN QUINOLIZIDINE AND INDOLIZIDINE SYSTEMS

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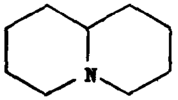
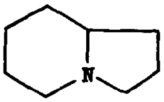
There is a literature conflict regarding the position of the conformational equilibrium of the ring fusion of quinolizidine (cf., I) an important heterocyclic nucleus (1). Thus, a

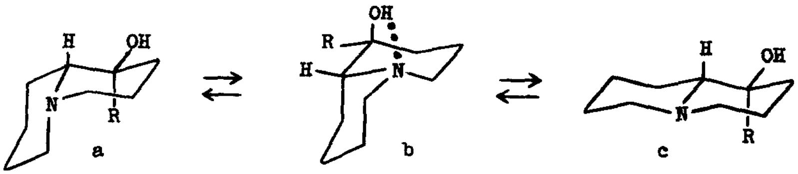


quinolizidine



indolizidine

$-\Delta G°_Q$ value (2) of 4.4 has been kinetically derived (3), while values of 4.6 (4) and 2.6 (5) have been suggested, both from analogy to the decalin system. The higher values appear to be generally accepted (6). We now conclude, however, that the 4.6 value was improperly deduced, because [as in an earlier deduction (7)] only the 1,3-diaxial hydrogen-hydrogen interactions were considered. When the comparable (8) 1,2-skew interactions are also considered (9), $-\Delta G°_Q$ should correspond to that of the decalins [$\sim$2.6 kcal/mole (10)], if small differences in the geometry of the two systems may be ignored.



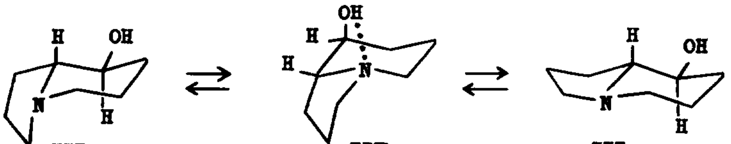
I, R = H; II, R = phenyl

Although this analysis suggests a correspondence between the $-\Delta G°$ values of these two systems, it does not prove the case. Indeed, a contrary conclusion is suggested by analogy to the indolizidine-hydrindane relationship, where spectral data have established (4) (reaffirmed below) that indolizidine is significantly more stable in a <u>trans</u> ring fusion than is hydrindane, its carbocyclic analog [$-\Delta G° \sim 0.3$ kcal/mole (11)].

The issue could best be settled by a spectroscopic determination of $-\Delta G°_Q$. To date,

however, exclusively cis or trans quinolizidines have been recognized from ir and nmr studies. We now report the first direct observation of some quinolizidine equilibria, and offer a preliminary interpretation of the results.

Dilute solution ir spectra (Fig. 1) of 1-hydroxy-1-(phenyl-t-10-H)quinolizidine (12) (II), have been recorded under the usual conditions (13), and earlier studies (14) of the B epimers of 1-hydroxyquinolizidine (I) and 8-hydroxyindolizidine (III) have been extended, through the use of 50 and 100 mm cells. For II, two hydroxyl bands at 3475 (intramolecularly bonded OH···N) and 3609 cm^{-1} were observed, the ϵ_{max} values of which were concentration independent on further dilution. These bands are unquestionably due to the equilibrium IIb (40%) $\rightleftarrows$ IIc (60%). The percentage of IIc is calculated from the integrated area of the 3609 band, relative to that of either α-phenylethanol or 1-methyl-4-hydroxy-4-phenylpiperidine as models, while IIb = 100-IIc. In the case of I and III, small bands at 3520 (Ib, 2%) and 3530 cm^{-1} (IIIb, 3%), not previously apparent, were revealed with the aid of the very long path cells. Here, the minor concentrations are assigned from the extinction coefficients of the bonded bands, relative to that of their corresponding hydroxyl epimers [100% bonded models (14)].



IIIa IIIb IIIc

The above assignments are based upon the purity of the compounds (glpc), the position and apparent concentration independence of the bands (in dilute solution), and from the fact that they disappeared when a drop of deuterium oxide was added to effect OH→OD exchange (15). When a minor correction (16) for the presence of cis fused free OH species Ia and IIIa is made, one obtains total cis fused populations of about 3% (for I) and 4% (III), which correspond to $-\Delta G^\circ$ values of 2.1 for I and 1.9 for III. For unsubstituted quinolizidine and indolizidine, values of $-\Delta G^\circ_Q = 2.6$ and $-\Delta G^\circ_{In} = 2.4$ are obtained, if one allows for a 0.5 kcal/mole contribution (16) due to the intramolecular hydrogen bond ($-\Delta G^\circ_{OH\cdots N}$) and neglects small entropy differences. The $-\Delta G^\circ_Q$ value calculated from the equilibrium of II agrees with this result, although this conformational analysis bears an added uncertainty inherent in the approximation of several interaction energies, not required for I (or III). The essential equality of $-\Delta G^\circ_Q$ and $-\Delta G^\circ_{In}$ contrasts with the > 2.0 kcal/mole difference between their two carbocyclic analogs. We cannot explain this apparent anomaly.

We intend to test these results by a rigorous evaluation of the crucial $-\Delta G^\circ_{OH\cdots N}$. The unequivocal determination of $-\Delta G^\circ_Q$ has an important bearing on the conformational assignments of many substituted quinolizidine systems, to be given detailed attention at a later date.

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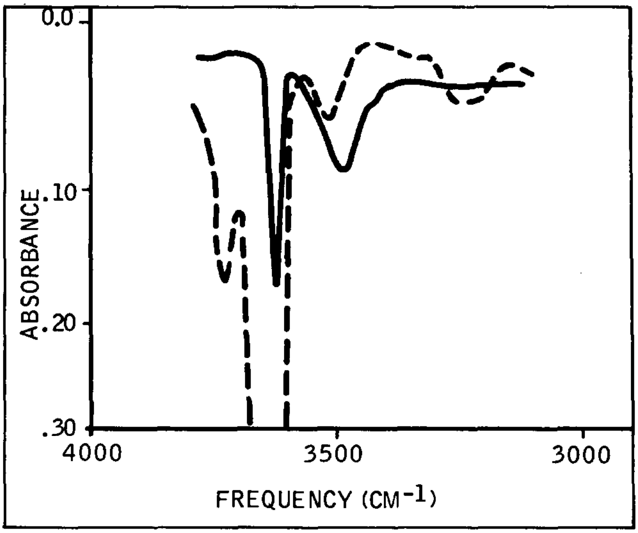
Figure 1

Dilute Solution Infrared Spectra



– – – Compound I, 0.006 M CCl_4 solution, 10 cm.

——— Compound II, 0.002 M CCl_4 solution, 2 cm.

(For I, the small band near 3700 cm^{-1} is due to traces of water, that at 3225 cm^{-1} undoubtedly to a few percent of persistent dimer.)

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