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CONFORMATIONAL ANALYSIS OF INTRAMOLECULAR BONDED AMINO ALCOHOLS

THE CONFORMATIONAL FREE ENERGIES OF SOME INTRAMOLECULAR OH · · · N HYDROGEN BONDS[1]

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Abstract—Equilibrium positions between intramolecular OH · · · N hydrogen bonded and free OH forms of some 3-piperidinols, decahydroisoquinolinols, a decahydroquinolinol, lupinine and N-methyl-3-piperidinemethanol have been determined from dilute solution IR spectral data at 33°. Conformational free energies of the H-bonds ($\Delta G^{\circ}_{OH \cdot N}$, attractive) have been calculated. The results suggest a linear relationship between the apparent value of $\Delta G^{\circ}_{OH \cdot N}$, as defined by the method of calculation, and the strength of the OH · · · N bond expressed as $\Delta\nu$, within the limits of 0·5 ± 0·2 kcal/mole per 100 cm^{-1}, from $\Delta\nu$ 90 to 350 cm^{-1}. For *cis*-decahydroisoquinoline (N-Me or N-H) systems, a 0·4 kcal/mole difference has been calculated between the two possible ring-fused conformations, in favor of the so-called steroid form. For the corresponding *cis*-decahydroquinoline equilibrium, a 0·8 kcal/mole difference has been calculated, in favor of the nonsteroid form.

Configurations of intramolecular H-bonded amino alcohols have been conveniently assigned from their IR spectra in dilute solution, where intermolecular H-bonding is eliminated.[2] Recently, from quantitative analysis of IR data, the equilibrium positions between bonded (OH · · · N) and free OH forms of several azabicyclic alcohols were assigned.[3] We now present the results of our study of other H-bonded amino alcohols, and calculate the conformational free energies of their intramolecular H-bonds.

RESULTS

Relative populations of free and bonded OH groups in conformational equilibria, if reported at all in the literature, are invariably given as qualitative assignments based on comparative IR molecular absorptivity coefficients (ϵ). The latter are not generally suited for quantitative assignments, since they are known to vary markedly, even for members of an epimeric pair.[3a] Unlike ϵ, however, the molar free ν_{OH} band area (B) is relatively constant for similar compounds.[4] Thus, we have found[3a] a ν_{OH} band area of 3200 ± 200 l $mole^{-1}$ cm^{-2} for a series of cyclic secondary alcohols (100% free OH) in dilute carbon tetrachloride solution. A nitrogen in the ring, two or three atoms removed from the carbinol group, appears not to affect this value. Thus, for compounds in mobile equilibrium between a bonded and one or more free OH forms, the percentage of total free OH species in the equilibrium may be assigned from its free OH band area, relative to that of a model reference compound containing 100% free OH.[3] The percentage of the bonded form, therefore, is simply 100% minus the percentage of free OH.

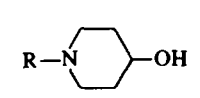
Table 1 gives the pertinent spectral data and experimental results for the amino alcohols we have studied, all of which are named in the Experimental. From these limited data, it appears that the B values of compounds with 100% free OH increase in the order: tertiary, secondary, primary OH group. In addition, the ν_{OH} area is apparently larger (from the data of **4**) in carbon tetrachloride than in tetrachloroethylene solution.

The probable error of the molar percentages assigned in Table 1 is a function of the probable error of the measured free OH band area of both the compound and its model reference, and upon the inherent suitability of the reference compound to serve as the free OH model. As indicated above, the B values of the reference models are believed to be valid, at least to within a reliability of 200 l $mole^{-1}$ cm^{-2}. Hence, a hypothetical B value of 1600 l $mole^{-1}$ cm^{-2} (assumed to be accurately measured to within about ± 100 l $mole^{-1}$ cm^{-2}), relative to 3200 ± 200 l $mole^{-1}$ cm^{-2} for its 100% free OH model, corresponds to 50 ± 5 mole-% free OH. Thus, while larger probable errors are possible, the mole-percentages given in Table 1 are estimated to be reliable to within about ± 5 units (hopefully better) over the range of values given. This conclusion is supported by the internal consistency of the results calculated below on the basis of these assign-

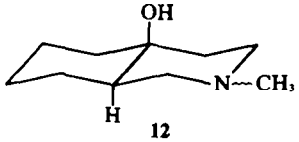
Table 1. IR spectral data[a] from amino alcohols at 33 ± 2°

Intramolecular bonded amino alcohols					100% free-OH, reference amino alcohols*		
Cpd No.	ν_{OH} cm^{-1} Free	ν_{OH} cm^{-1} Bonded	Area of free OH band (B) (1 mole^{-1} cm^{-2})	% Free OH	Cpd No.	ν_{OH} (cm^{-1})	Band area (B) (1 mole^{-1} cm^{-2})
1	3627	3539	1350	43	2	3626	3150
3	3626	3534	1700	55	4	3624	3100
5	3633[b]	3532[b]	735[b]	26	4	3622[b]	2800[b]
11	3606	3514	725	32	12	3621	2300
13	3624[b]	3531[b]	1430[b]	56	4	3622[b]	2560[b]
14	3624[b]	3531[b]	2140[b]	84	4	3622[b]	2560[b]
15	3625	3320	500	16	16	3633[c]	3200
17	3625	3282	125	4	16	3633[c]	3200
18	3641	3290	440	11	19	3641	3850
20	3643	3295	2800	73	19	3641	3850

[a] In dilute CCl_4, unless otherwise indicated. All compounds are named in the Experimental.
[b] Tetrachloroethylene.
[c] Shoulder at 3609 cm^{-1}.
*Reference compounds cited in Table 1:



2: R = CH_3; 4: R = H



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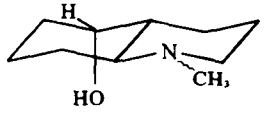

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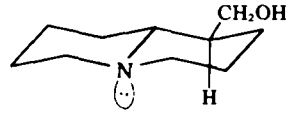

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ments, and their agreement with literature results, where available, as derived by other means. Conversely, the method given below appears to be applicable to the semiquantitative analysis of conformational equilibria in intramolecular OH · · · N bonded systems.*

In the following discussion, $\Delta\nu$ (cm^{-1}) refers to the difference between ν_{OH} of the free and bonded OH forms in the equilibrium.

*After these results were submitted for publication it was brought to our attention that an IR study of 3-piperidinol systems, by Tichy *et al.*, had been published[5] at the same time our results were submitted. While differing somewhat in the theoretical treatment, we are in general qualitative agreement with their results. We differ, however, in certain quantitative aspects, notably in the assignment of the N-methyl-3-piperidinol equilibrium. Although Tichy *et al.* report their spectral data for both the free and bonded OH bands, they make their equilibrium assignments from the area of the bonded OH · · · N band, using a model containing 100% bonded OH · · · N groups. In contrast to the free OH band, however, the bonded OH band produces a larger molar area, which appears to be more variable, and which tends to increase with increasing strength of the H-bond. Thus, while the B value of the latter might be a linear function of the mole-% bonded OH · · · N species for closely related compounds, in our view an assignment based on the bonded OH band area is less reliable than that based on the free OH band. Indeed, if their N-methyl-3-piperidinol assignment is taken from their free OH band data, one obtains a result (36% free OH) that agrees (within experimental error) with our assignment (43% free OH, **1**, Table 1) for this compound.

DISCUSSION

3-Piperidinols are known[6] to form an intramolecular H-bond. We find that N - methyl - 3 - piperidinol (**1**) exists as 43% free OH species **1a*** (two forms)† and **1c**, in equilibrium with 57% of a bonded species, **1b**.‡

Before analyzing this result, let us first define the conformational equilibrium of any system by the free energy difference between conformations, by:

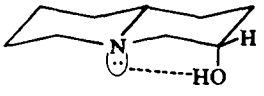
$$-RT \ln (\text{product})/(\text{educt}) = \Delta G^\circ_{\text{product}} - \Delta G^\circ_{\text{educt}} \quad (1)$$

where ΔG° of each species is assumed[9] to be equal to the algebraic sum of its individual confor-

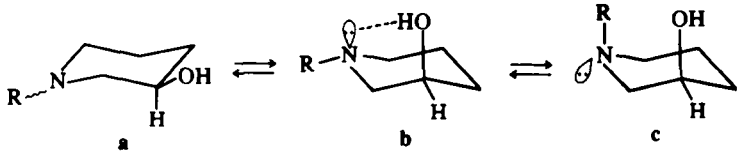
*A value of 60% **1a** has been calculated[7] from NMR data, for a 30% solution. At this concentration, however, intermolecular H-bonding should shift the equilibrium toward the equatorial OH species (**1a**), compared to that in the dilute solution used for recording the IR spectrum.

†While it is understood that two forms (N-R axial and equatorial) exist in **1a** (and in other compounds discussed below) due to inversion at the nitrogen atom, these are not separately considered in this discussion.

‡A possible nonbonded form (*i.e.* free OH rotamer) of **1b** (also for **5b**, below) is excluded based on the spectral data of the geometrically related quinolizidinols (*e.g.* **i**), where, with a comparably strong hydrogen bond ($\Delta\nu \sim$ 90 cm^{-1}) and a fixed diaxial OH/N-electron pair conformation, no free OH rotamer species was observed.[8]



(i)



1: R = CH_3; 3: R = H

mational interactions. From equation (1), repulsive interactions are defined as positive, attractive interactions negative, in sign.

In the **1** equilibrium, **1c** may be ignored, since it is undoubtedly too small to be significant, due to the probable energy of the *syn*-axial[10] Me/OH interaction.[11,*] From conformational analysis, **1b** is seen to be opposed by one *syn*-axial OH/H interaction (symbolized by $\Delta G^{\circ}_{H/OH}$), but is presumably favored by the contribution of the OH···N hydrogen bond ($\Delta G^{\circ}_{OH\cdots N}$). Therefore, if the conformational interactions in **1b** are defined relative to those in **1a** taken equal to zero, the **1a**, **1b** relationship may be calculated, to a first approximation (ignoring[13] the steric contribution, if any, of a *syn*-axial H/N-electron pair), from equation (1), by:

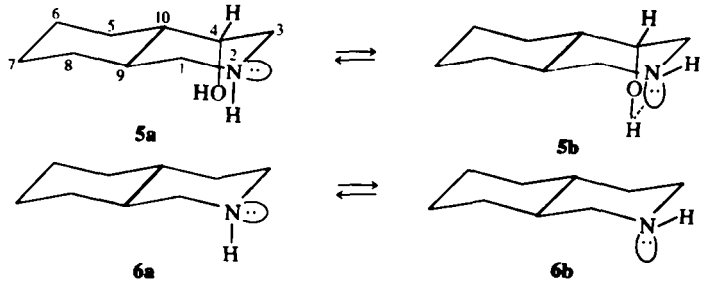
$$-RT \ln (\mathbf{1b})/(\mathbf{1a}) = (\Delta G^{\circ}_{H/OH} - \Delta G^{\circ}_{OH\cdots N})_{1b} \quad (2)$$

Substituting the values of 57% for **1b** and 43% for **1a**, and, assuming that a single *syn*-axial H/OH interaction on a piperidine ring is comparable to that of cyclohexanol,[14] for $\Delta G^{\circ}_{H/OH}$ 0·35 kcal/mole (from one half the conformational value of the OH group in aprotic solvents[15]), $\Delta G^{\circ}_{OH\cdots N}$ is calculated to be 0·5 kcal/mole (in favor of **1b**) for this hydrogen bond ($\Delta\nu$ 88 cm^{-1}).

For a similar analysis of the 3-piperidinol (**3**) equilibrium, however the population of **3c**† must be taken into account. Thus, from the **3b**/**3c** ratio, which may be experimentally obtained (see below) directly from **5b**/**5a**, **3c** is calculated to be 16%, hence **3a** is equal to 39% (55–16%). Then, from the relationship between **3b** (45%) and **3a**, defined as in (2), above, $\Delta G^{\circ}_{OH\cdots N}$ is calculated equal to about 0·45 kcal/mole for the **3** hydrogen bond ($\Delta\nu$ 92 cm^{-1}).

The $\Delta G^{\circ}_{OH\cdots N}$ values obtained above for **1** and **3** are *apparent* values that are a function of the method by which they have been derived. Thus, as calculated, the entropy of mixing contribution due to the two N–R forms (in **a**) was ignored, as was the effect (if any) of the nitrogen electron pair. In addition, the results also depend upon the assigned value of $\Delta G^{\circ}_{H/OH}$ in these systems. It is interesting to find, therefore, that for **1b** and **3b**, which contain hydrogen bonds of equal strength as measured by $\Delta\nu$,[17] the same apparent $\Delta G^{\circ}_{OH\cdots N}$ value was obtained, within the probable error of the experimental method. Moreover, this value appears to be very useful for the conformational analysis of heterocyclic systems, when applied in a consistent manner, as shown below.

trans-*Decahydroisoquinolin-4α-ol* (**5**). The IR data shows (Fig 1) that this compound[18] exists in equilibrium between a free **5a** and a bonded **5b** form, depending upon the orientation of the N–H/N-electron pair. Qualitatively speaking, it is interesting to note that a significant population (26%) of free OH species (**5a**, N–H axial) is observed in this system (Table 1), notwithstanding the driving force of the intramolecular H-bond, in favor of **5b**.



*Also, no free OH for a *syn*-axial Me/OH form (corresponding to **1c**) was observed in the IR spectrum of *trans*-N-methyldecahydroisoquinolin-9-ol.[12a]

†The small free OH band observed in the IR spectrum of methyl carpamate[16a] (and other all-*cis*-2,6-dialkyl-3-piperidinols[16b]) is apparently due to a *syn*-axial NH/OH form corresponding to **3c**.

From this result, we conclude that in the corresponding equilibrium of the unsubstituted *trans*-decahydroisoquinoline system (**6**), less than 74% of the NH equatorial form (**6b**) must be present. However, the above result does not prove the exact position of the **6** equilibrium, hence is not directly applicable to the controversy[19] over whether

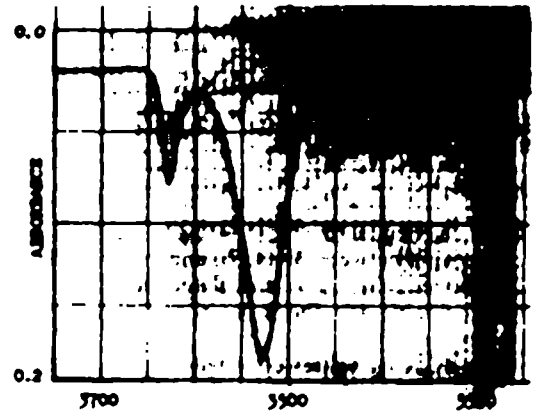


Fig 1. *trans* - Decahydroisoquinolin - 4α - ol (**5**) (0·00238 M, tetrachloroethylene, 2 cm)

the NH axial or NH equatorial conformation is preferred, due to the uncertainty, in **5a**, of the value of the *syn*-axial NH/OH interaction. The latter is possibly even weakly attractive, due to a (presumed) NH···O H-bond. Nevertheless, the result for **5** is directly applicable to the analysis (above) of the 3-piperindinol system (**3**), and, below, for the *cis*-decahydroisoquinolin-4-ols. Thus, as for **1** and **3**, the **5** equilibrium may be defined according to (1), by:

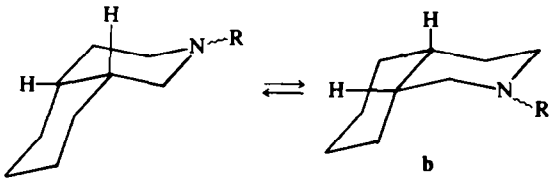
$$-RT \ln (\mathbf{5b})/(\mathbf{5a}) = (2\,\Delta G^{\circ}_{H/OH} - \Delta G^{\circ}_{OH\cdots N})_{5b} - (2\,\Delta G^{\circ}_{H/OH} + \Delta G^{\circ}_{OH/NH})_{5a} \quad (3)$$

which reduces to:

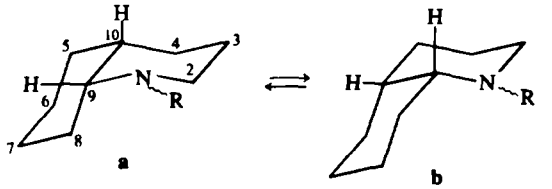
$$RT \ln (\mathbf{5b})/(\mathbf{5a}) = \Delta G^{\circ}_{OH\cdots N} + \Delta G^{\circ}_{OH/NH}. \quad (3')$$

A similar analysis of **3** shows that the **3b/3c** ratio is defined by the identical expression. Therefore, the latter (hence the percent **3c**) may be taken directly from the **5b/5a** ratio, independent of the actual values of the conformational interactions, assuming only that they are essentially equal (if not identical) in both systems.

cis-Decahydroisoquinoline (**7**) *and cis-Decahydroquinoline* (**9**) *systems.* The two parent compounds and their N-Me analogs both exist in equilibrium between a so-called steroid (**7** and **8**, **b**; **9** and **10**, **a**) and a nonsteroid form.



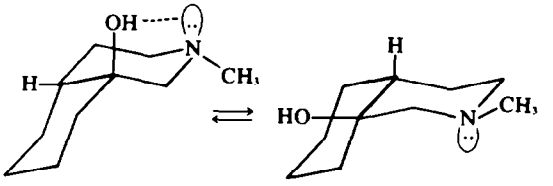
7: R = H
8: R = CH_3



9: R = H
10: R = CH_3

In other studies,[20] it was concluded that *cis*-decahydroquinoline systems (**9** and **10**) preferably exist (by perhaps 85%, if not more) in the nonsteroid (**b**) form. The *cis*-decahydroisoquinoline system appears not to have been similarly studied.

For the conformational analysis of these systems, let us first consider *cis* - N - methyldecahydroisoquinolin - 9 - ol (**11**). This compound exists in an **11a/11b** equilibrium,[12] assigned (IR) as a 68/32 mixture,* respectively.



The equilibrium may then be defined on the basis of the *syn*-axial interactions (as for **1**, above) according to (1), by:

$$-RT \ln (\mathbf{11b})/(\mathbf{11a}) = (2\,\Delta G^{\circ}_{CH_2/H} + \Delta G^{\circ}_{CH_2/N} + 2\,\Delta G^{\circ}_{H/OH})_{11b} - (3\,\Delta G^{\circ}_{CH_2/H} + \Delta G^{\circ}_{H/OH} - \Delta G^{\circ}_{OH\cdots N})_{11a}. \quad (4)$$

Here, a $\Delta G^{\circ}_{OH\cdots N}$ value of 0·5 kcal/mole, calculated for **1b**, is assumed to be applicable, because the H-bonds in both **1b** and **11a** have the same stereochemical relationship, and are of equal strength ($\Delta\nu$ 90 ± 2 cm^{-1}). As for **1** and **3**, $\Delta G^{\circ}_{H/OH}$ is taken to be 0·35 kcal/mole.† On substituting the value of each term given above into (4), the value of a *syn*-axial interaction of a CH_2 with the N-electron pair ($\Delta G^{\circ}_{CH_2/N}$) is calculated to be 0·45 kcal/mole

*This ratio was calculated using the B value of **12** (structure in footnote to Table 1) as a reference model with 100% free OH. For tertiary OH **12**, the B value was found to be smaller than that of the model secondary alcohols examined. For comparison to a second model, the value for 4-quinclidinol (**24**) (the closest analog of this bridgehead structural type available to us) was also measured; its B value (2600 l $mole^{-1}$ cm^{-2}) was found to be comparable to that of **12**.

†A conformational value ($2\,\Delta G^{\circ}_{H/OH}$) of 0·94 kcal/mole has been reported [12b] for a decahydroisoquinolinol in aqueous solution. However, this value would be smaller in aprotic media.[11a]

(repulsion) in **11b**. Here too, the result is an apparent value, which is dependent (mainly) upon that taken for $\Delta G^{\circ}_{OH\cdots N}$. Based on this result, the conformational equilibrium of the unsubstituted parent (ΔG°_{ii}) defined by:

$$-RT \ln (\mathbf{8b})/(\mathbf{8a}) = (2\,\Delta G^{\circ}_{CH_2/H} + \Delta G^{\circ}_{CH_2/N})_{8b} - (3\,\Delta G^{\circ}_{CH_2/H})_{8a} \quad (5)$$

is calculated to favor the steroid form (**8b**) by 0·4 kcal/mole (about 66% at 33°). As shown below, the same result is also calculated (from **13**) for the **7b/7a** system.

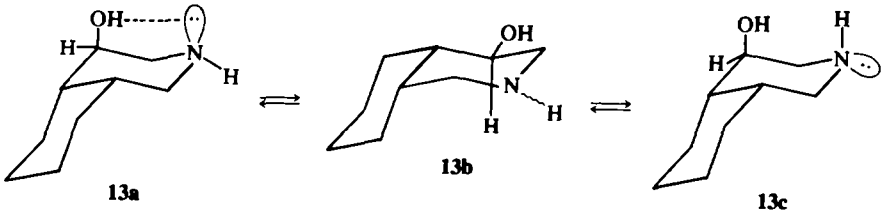
Similarly, the decahydroquinoline systems (**9** and **10**) defined (for **10**) by:

$$-RT \ln (\mathbf{10b})/(\mathbf{10a}) = (\Delta G^{\circ}_{CH_2/H} + 2\,\Delta G^{\circ}_{CH_2/N})_{10b} - (3\,\Delta G^{\circ}_{CH_2/H})_{10a} \quad (6)$$

are calculated to favor the nonsteroid form (**b**) by about 80% (0·8 kcal/mole) at 33°, in good qualitative agreement with the conclusion reached by others.[20]

The dilute solution infrared spectra of the *cis* - decahydroisoquinolin - 4β - ol (**13**) and 4α - ol (**14**) epimers have been published, and their relative configurations assigned.[21] A quantitative analysis of the data is given below.

The IR data shows that **13** exists in an equilibrium between 44% bonded (**13a**) and 56% free OH forms, assigned as a mixture of **13b** and **13c**.

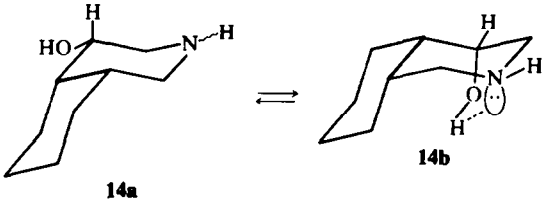


The percentage of **13c** may be assigned from the results of **5**, above. Thus, from the **5a/5b** equilibrium, one calculates a 15 mole-% [(26/74) × 44] concentration for **13c** in the corresponding **13a/13c** equilibrium, leaving **13b** equal to 41 mole-% (56–15%). From conformational analysis, **13a** has one *syn*-axial OH/H interaction, while in **13b**, the interaction of the OH Group with the 5α hydrogen is also equivalent to a *syn*-axial OH/H interaction. The equilibrium between **13a** and **13b**, therefore, may be defined by:

$$-RT \ln (\mathbf{13b})/(\mathbf{13a}) = (2\,\Delta G^{\circ}_{CH_2/H} + \Delta G^{\circ}_{CH_2/N} + \Delta G^{\circ}_{H/OH})_{13b} - (3\,\Delta G^{\circ}_{CH_2/H} + \Delta G^{\circ}_{H/OH} - \Delta G^{\circ}_{OH\cdots N})_{13a}. \quad (7)$$

Subtracting, then substituting for each term (for $\Delta G^{\circ}_{OH\cdots N}$ 0·45 kcal/mole, from **3**, above) gives $\Delta G^{\circ}_{CH_2/N}$ 0·45 kcal/mole in **13b**. The unsubstituted, parent (**7**), therefore, is calculated from equation (5) to favor the steroid form (**7b**) by 0·4 kcal/mole, the same as calculated above for the N-Me analog (**8**).

In contrast to **13**, the IR data show **14** to exist as only 16% of a bonded form (**14b**). This result is apparently due to two *syn*-axial OH/CH_2 interactions in **14b**, which force the equilibrium predominantly to the side of the free OH species **14a** (84%). The relative configurations of **13** and **14** were assigned on the basis of this distinction.[21] From conformational analysis, the value of these OH/CH_2 interactions ($\Delta G^{\circ}_{CH_2/OH}$) may be calculated.



14a **14b**

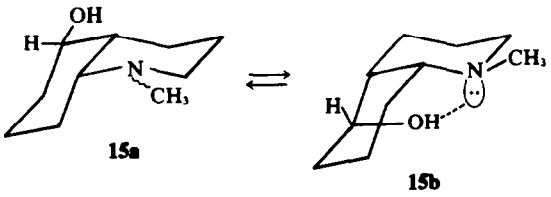
In **14a**, the interaction of the OH group with the 5β hydrogen is equivalent to a *syn*-axial H/OH interaction. Therefore, the **14** equilibrium may be defined by:

$$-RT \ln (\mathbf{14b})/(\mathbf{14a}) = (2\,\Delta G^{\circ}_{CH_2/OH} + \Delta G^{\circ}_{CH_2/N} - \Delta G^{\circ}_{OH\cdots N})_{14b} - (3\Delta G^{\circ}_{CH_2/H} + \Delta G^{\circ}_{H/OH})_{14a}. \quad (8)$$

Substituting for each term the values given above, and for $\Delta G^{\circ}_{OH\cdots N}$ 0·45 kcal/mole (from **3**), $\Delta G^{\circ}_{CH_2/OH}$ is calculated to be 2·0 kcal/mole, in very good agreement with the value found in cyclohexane systems.[11] Or, conversely, based on the spectral data, the calculated value of $\Delta G^{\circ}_{OH\cdots N}$ in **14b** is in excellent agreement with that of corresponding systems of the same $\Delta\nu$, when the other interactions are all assigned on the basis of current conformational theory.

By applying the above results to an analysis of *cis* - N - methyldecahydroquinolin - 5α - ol (**15**) and *cis* - N - methyldecahydroisoquinolin - 8α - ol (**17**), $\Delta G^{\circ}_{OH\cdots N}$ values of stronger hydrogen bonded systems may be calculated. The **15** equilibrium (16% **15a**, 84% **15b**), may be defined by:

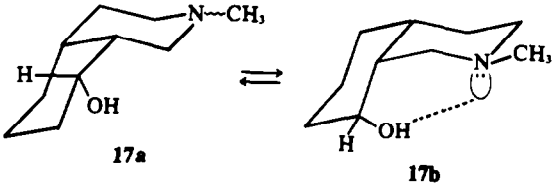
$$-RT \ln (\mathbf{15b})/(\mathbf{15a}) = (\Delta G^{\circ}_{CH_2/OH} + \Delta G^{\circ}_{CH_2/N} + \Delta G^{\circ}_{H/OH} - \Delta G^{\circ}_{OH\cdots N})_{15b} - (3\,\Delta G^{\circ}_{CH_2/H} + \Delta G^{\circ}_{H/OH})_{15a} \quad (9)$$



15a 15b

based on the conclusion that in **15a**, the interaction of the hydroxyl group with the 4β hydrogen is equivalent to a *syn*-axial OH/H interaction. Subtracting and then substituting for each remaining term in (9) gives $\Delta G^\circ_{OH\cdots N}$ 0·9 kcal/mole for **15b** ($\Delta\nu$ 305 cm^{-1}).

Similarly, the 17 equilibrium (4% **17a**, 96% **17b**),



17a 17b

defined by:

$$-RT\ln(\mathbf{17b})/(\mathbf{17a}) = (\Delta G^\circ_{CH_2/OH} + \Delta G^\circ_{CH_2/H} + \Delta G^\circ_{H/OH} - \Delta G^\circ_{OH\cdots N})_{17b} - (3\,\Delta G^\circ_{CH_2/H} + \Delta G^\circ_{H/OH})_{17a} \quad (10)$$

gives $\Delta G^\circ_{OH\cdots N}$ 2·3 kcal/mole in **17b** ($\Delta\nu$ 343 cm^{-1}). In this case, however, the uncertainty in the result is large, due to the probable error in the value of **17a**, as determined from the very small free OH band observed.

Intramolecular $-CH_2OH\cdots N$ *bonded systems.* These systems, also, are amenable to analysis by the principles discussed above. Thus, lupinine (**18**), which forms a strong intramolecular H-bond, is assigned as a mixture of 11% free OH species **18a** and **18b** (conformational rotamers, shown in Newman projection) and 89% bonded species **18c**.*

From examination of Dreiding models, the conformational interactions of the CH_2OH group in these three species are seen to be essentially equivalent to the typical diaxial interactions, as defined and assigned above. Thus, the **18a**, **18b** equilibrium is defined by:

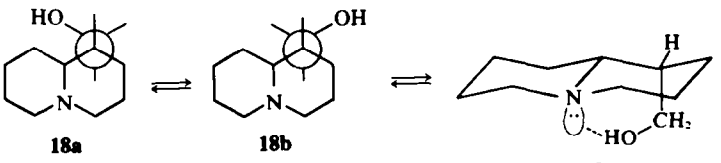
$$-RT\ln(\mathbf{18b})/(\mathbf{18a}) = (2\,\Delta G^\circ_{CH_2/H} + \Delta G^\circ_{CH_2/N:} + \Delta G^\circ_{OH/H})_{18b} - (\Delta G^\circ_{CH_2/OH} + \Delta G^\circ_{CH_2/N:} + \Delta G^\circ_{CH_2/H})_{18a}. \quad (11)$$

Substituting the value of each term gives 0·8 kcal/mole in favor of **18b**, which corresponds to a free OH mixture (11%) of about 2% **18a** and 9% **18b**. Then, from the **18b**, **18c** equilibrium, defined by:

$$-RT\ln(\mathbf{18b})/(\mathbf{18c}) = \Delta G^\circ_{18b} - (\Delta G^\circ_{CH_2/OH} + \Delta G^\circ_{CH_2/H} - \Delta G^\circ_{OH\cdots N})_{18c} \quad (12)$$

one calculates $\Delta G^\circ_{OH\cdots N}$ 1·8 kcal/mole ($\Delta\nu$ 350 cm^{-1}).

N-methyl 3-piperidinemethanol (**20**), similarly examined, may be assigned as a mixture of 73% free OH species **20a** and **20c**, and 27% bonded specie **20b**. In addition, as for the species with the free OH in lupinine, **20a** is seen (from the model) to consist of two equivalent —CH_2OH rotamer forms, and **20c** of three rotamer forms, two of which are



18a 18b 18c

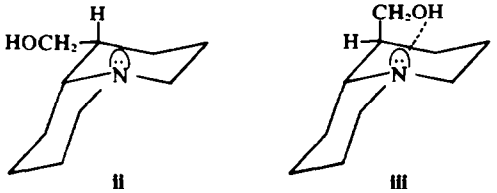
equivalent and more favored than the third. The conformational interactions in each rotamer form of **20a** may be calculated, to a first approximation, from:

$$\Delta G^\circ_{20a} = (\Delta G^\circ_{CH_2/H} + \Delta G^\circ_{CH_2/N\cdot} + \Delta G^\circ_{H/OH})_{20a}. \quad (13)$$

Similarly, the corresponding conformational value for each of the two equivalent forms of **20c** is calculated equal to $\Delta G^\circ_{H/OH}$, while that of the less favored form of **20c**, to $2\,\Delta G^\circ_{H/OH}$.

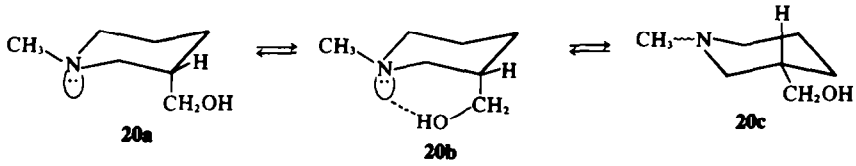
Defining the relationship between the rotamers of **20a** and **20c** according to equation (1) and substituting the values of each conformational interaction as above, the species with free OH in **20** (73%) is calculated to consist of 6% **20a** (3% for each rotamer form) and 67% **20c** (26, 26 and 15% rotamer

*The possibility that the lupinine free OH band might be due to the presence of a *cis*-quinolizidine conformation (ii) is excluded by conformational analysis, since,



ii iii

apart from other interactions, a *cis*-quinolizidine ring fusion is inherently about 2·6 kcal/mole less stable than the *trans*.[3b] In agreement with this conclusion, epilupinine (**19** in footnote to Table 1) shows no evidence of intramolecular hydrogen bonding corresponding to a *cis*-quinolizidine form (iii), in spite of the strong OH···N bond that would be formed.



composition, respectively). Therefore, from the equilibrium between **20b** (27%) and each form of **20a** (3%), defined by:

$$-RT \ln (\mathbf{20b})/(\mathbf{20a}) = (\Delta G^{\circ}_{CH_3/OH} - \Delta G^{\circ}_{OH\cdots N})_{\mathbf{20b}} - \Delta G^{\circ}_{\mathbf{20a}} \quad (14)$$

one calculates $\Delta G^{\circ}_{OH\cdots N}$ 1·7 kcal/mole ($\Delta\nu$ 350 cm^{-1}). In this case, both species respresent a single NMe form. The same result is obtained, however, when $\Delta G^{\circ}_{OH\cdots N}$ is calculated from the relationship between either rotamer form of **20c** (two N-Me forms in each rotamer, not separately considered) and **20b**.

Correlation of $\Delta G^{\circ}_{OH\cdots N}$ *with* $\Delta\nu$. For the systems presented above, the values calculated for $\Delta G^{\circ}_{OH\cdots N}$ follow the order of increasing strength of the H-bond, as measured by $\Delta\nu$. Indeed, the results present a relatively linear correlation of $\Delta G^{\circ}_{OH\cdots N}$ and $\Delta\nu$, which is bracketed by an assigned value of $\Delta G^{\circ}_{OH\cdots N}$ of 0·5 ± 0·2 kcal/mole per 100 cm^{-1} $\Delta\nu$, for all of these compounds. This correlation is summarized in Table 2.

In earlier studies, it was suggested that $\Delta\nu$ may be a linear function of the enthalpy ($\Delta H°$) of the H-bond.[17,22] However, $\Delta\nu$ is now believed to be dependent upon several variables, as recently summarized,[23] plus, for OH···N systems, the relative basicity of the nitrogen atom.[24] Accordingly, deviations from linearity are known.[17,25] Nevertheless, correlations have been reported within structurally related series.[26] Therefore, we suggest that the relationship calculated above for $\Delta G^{\circ}_{OH\cdots N}$ and $\Delta\nu$ is due to a relatively linear relationship between $\Delta H°$ and $\Delta\nu$, and that entropy factors are relatively small within this series.

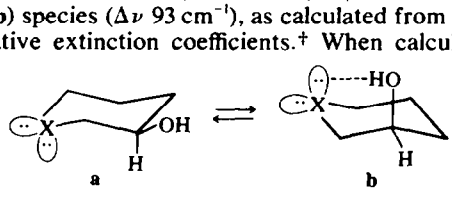
Table 2. Correlation of $\Delta G^{\circ}_{OH\cdots N}$ and $\Delta\nu$ for intramolecular bonded amino alcohols related to piperidine

$\Delta\nu$ (cm^{-1})	Assigned[a] $\Delta G^{\circ}_{OH\cdots N}$ (kcal/mole)	Calculated, by conformational analysis $\Delta G^{\circ}_{OH\cdots N}$ (kcal/mole)	Compound
100	0·5 ± 0·2	0·5, 0·45, 0·45	**1, 3, 14**
200	1·0 ± 0·4		
300	1·5 ± 0·6	0·9	**15**
350	1·8 ± 0·7	2·3, 1·8, 1·7	**17, 18, 20**

[a] Empirically assigned, assuming a linear relationship of 0·5 ± 0·2 kcal/mole per 100 cm^{-1} units of $\Delta\nu$ for all compounds.

Comparison of $\Delta G^{\circ}_{OH\cdots N}$ *to that of other H Bonded systems.* It is of interest to compare the $\Delta G^{\circ}_{OH\cdots N}$ values which we have calculated to those which have been reported (or may be calculated) for other types of intramolecular H-bonds. Our result for **1** is essentially equal to the 0·6 kcal/mole reported for the OH····NH_2 bond ($\Delta\nu \sim 100\ cm^{-1}$) in *trans* 2-aminocyclohexanol.[27] For the OH···OH bond in *trans* - 2 - cyclohexane - 1,2 - diol ($\Delta\nu \sim 40\ cm^{-1}$), 0·8 kcal/mole was found.[27] For an OH···O=C bond, ($\Delta\nu \sim 100\ cm^{-1}$), 3·5 kcal/mole has been calculated from a circular dichroism (c.d.) analysis.[28]*

Data have also been reported for the thia and oxa analogs of **1**.[29] Thus, tetrahydrothiopyran-3-ol (**21**) has been reported[29a] to exist as a 2/1 mixture ($\Delta G^{\circ}_{21} + 0·4$ kcal/mole) of free (**21a**) and bonded (**21b**) species ($\Delta\nu$ 93 cm^{-1}), as calculated from their relative extinction coefficients.† When calculated



21: X = S
22: X = O

according to equation (2), assigning $\Delta G^{\circ}_{H/OH}$ 0·35 kcal/mole, one obtains $\Delta G^{\circ}_{OH\cdots S} \sim 0·05$ kcal/mole, in favor of **21a**. This value corresponds to destabilizing (or, within experimental error, zero conformational) contribution for the **21b** intramolecular H-bond. This result is unreasonable, however, since the OH···S bond is strong enough to eliminate rotational conformers of the OH group in these systems, as shown by the spectrum of conformationally locked 3-phenyltetrahydrothiopyran-3-ol.[29a] Therefore, assuming the **21** equilibrium is correctly assigned, there appears to be an unevaluated factor that favors the equatorial OH form (**a**) in **21**, compared to that in **1** and **3**.

*The reported[28] IR data, however, suggest to us that a lower value might be a more reasonable result. Thus, from the IR results, 74% of a bonded species was calculated for (+)-1-hydroxydihydrocarvone in carbon tetrachloride, assuming an equal molar absorptivity for both the bonded and the free OH forms. A bonded OH group, however, generally gives a larger value than the same concentration of a non-bonded or less strongly bonded form.[2] Therefore, the concentration of the free OH species would be better calculated from comparison to a structurally related model compound containing 100% of its OH groups in this form.

†This method appears to be applicable to this system, based on footnote (15) in reference 29*a*.

The corresponding oxa analog **22**, which forms a relatively weak intramolecular hydrogen bond ($\Delta\nu$ 16 cm^{-1}),[29b] appears (to a first approximation, from relative extinction coefficients) to exist as a 44/56 mixture of **22a/22b**, which is almost the same as that found in **1**. When calculated according to equation (2), one obtains $\Delta G^{\circ}_{OH\cdot\ O}$ 0·5 kcal/mole. Apart from the entropy factor, this result, in comparison to $\Delta G^{\circ}_{OH\ N}$, parallels that drawn above from comparison of *trans* 2-cyclohexanediol to *trans* 2-aminocyclohexanol. That is, the OH····O intramolecular hydrogen bond seems to produce a greater apparent conformational driving force than the OH···N system, although the $\Delta\nu$ value of the latter may be considerably larger.

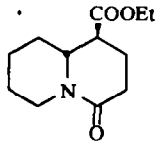
As might be expected, the ΔG° values for these varied intramolecular hydrogen bonds do not correlate, simply, with $\Delta\nu$. Additional comparisons between other systems, however, would be desirable.

EXPERIMENTAL

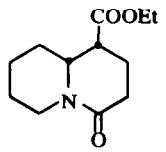
Spectra were recorded at about 0·0025 M as described[3a] at ambient temp in M. C. & B. Spectroquality CCl_4, dried over Linde Molecular Sieve 5A. The expanded scan was recorded after the soln had been in the instrument for about 20 min, and about 25 min was usually required to record the expanded band. Since the solutions tend to warm up while in the spectrometer beam, the expanded band was generally recorded at 33 ± 2°. All equilibrium data, therefore, were calculated for 33°. Band areas (B values, Table 1) were calculated as described,[3a] or by weighing cut-outs of Xerox copies of the plotted bands. In most cases, the free and bonded OH bands were completely separated. In some cases, however, (*e.g.* for **1** and **3**), the two bands overlapped in part, and had to be graphically separated. Customarily, the reference compound was recorded just before or after the sample being studied was recorded. For piperidin-4-ol (**4**), the two slightly different B values in tetrachloroetylene were obtained on different occasions. In one case, the spectrophotometer had just undergone extensive repairs.* Tetrachloroethylene (Eastman white label) was used as a solvent for **13** and **14**, because precipitation occurred in carbon tetrachloride. The tetrachloroethylene was passed over neutral alumina (Woelm) to remove ethanol stabilizer, then distilled onto 5A molecular sieve, and immediately used. The purity of each commercial sample was confirmed by GLPC on a Carbowax 20 M column.

N-Methylpiperidin-3-ol (**1**), redistilled before use, N-methylpiperidin-4-ol (**2**), piperidin-3-ol (**3**), and piperidin-4-ol (**4**) were purchased from the Aldrich Chemical Company, Milwaukee, Wisconsin. *trans*-Decahydroisoquinolin - 4α - ol (**5**),[18] *cis* - decahydroisoquinolin - 4β - ol (**13**) and its 4α-ol (**14**) epimer,[21] and *cis* - N - methyldecahydroisoquinolin - 8α - ol[30] (**17**) were kindly furnished by Professor Kimoto and Dr. Okamoto. *cis* - N - Methyldecahydroisoquinolin - 9 - ol (**11**) and its *trans* - 10 - ol (**12**) isomer,[12] and *cis*- (**15**) and *trans* - N - methyldecahydroquinolin - 5α - ol[31] (**16**) was kindly furnished by Professor G. Lupinine (**18**) was purchased from Mann Research Labs, New York, New York.

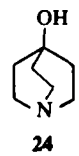
Epilupinine (**19**) was synthesized[32] by LAH reduction of 1 - carbethoxy - 4 - quinolizidone[33] (**23**). The racemic **19**, m.p. 80–81° (from light petroleum) (lit. m.p. 81°;[34] 82–83°[35]) was identified from its IR spectrum.[35] However, the literature reports that the hydride reduction of **23**, obtained by an alternate procedure, gives the epimeric lupinine.[36] Therefore, one concludes that in the former instance, intermediate **23** must have had the *trans* 1,10-H configuration (**23a**), while that from the alternate route,[36] the *cis*, 1,10-H configuration (**23b**).



23a



23b



24

N-Methyl-3-piperidinemethanol (**20**).[37] Ten grams of N-methyl-3-hydroxymethylpyridinium iodide, m.p. 75–76°, (lit[38] 82·5–84°) [from 3-pyridylmethanol (Aldrich Chem. Co.) and MeI in EtOAc] was hydrogenated over PtO_2 (0·033 g) in 200 ml abs EtOH for 12 hr at room temp at about 50 psig hydrogen in a Parr Hydrogenator. The soln was filtered to remove the catalyst, then concentrated on the rotary evaporator under reduced pressure. The residual oil was mixed with a soln of NaOH (2 g) in water (10 ml), then extracted with five 25-ml portions of ether. The extracts were dried (Drierite), concentrated and distilled to give 1·6 g of **20**, b.p. 88–90° (1·5–2·0 mm), $n_D^{22.5}$ 1·4765; methiodide, m.p. 214–215° (EtOH), (lit.[39], m.p. 215·4–216·6°). The product appeared to be pure by GLPC on a Carbowax 20 M column.

4-Quinuclidinol (**24**), available in our laboratory from another project, was examined by IR, to determine its B value for comparison to that of **12**. The compound, prepared[40] as described,[41] was found to melt higher than had been reported. Thus, **24**, obtained as white glistening needles on recrystallization from sodium dried benzene, melted at 215–216°, capillary tube (lit.[41] m.p. 155–160°, after sublimation of a small sample); m.p. ~ 150–160° (Fisher–Johns block). (Found: C, 66·0; H, 10·3; N, 11·2. Calcd for $C_7H_{13}NO$: C, 66·1; H, 10·3; N, 11·0%). It gave a single peak on GLPC. NMR (D_2O) δ 1·59 and 2·93, two asymmetrical triplets of equal areas. A small sample that was purified only by sublimation contained a minor component that was eluted (GLPC) before the main peak, but which was absent after recrystallization. The **24** dilute solution IR spectrum was measured in our laboratory: ν_{OH} 3608 cm^{-1}, ϵ 60 l $mole^{-1}$ cm^{-1}, B 2600 l $mole^{-1}$ cm^{-2}.

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*Based on a comparison of reported[3-5] data, the absolute value of the molar free OH band area appears to vary with the spectrometer used. Since mole-percent assignments are based upon comparison of relative areas, however, the instrumental factor should cancel out.

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