Unusually Strong Dependence of Conformation on Solvent

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Abstract: Relative partition coefficients between aqueous methanol and pentane of the two stereoisomers of a series of 4-*tert*-butylcyclohexylamines were measured by NMR. The cis isomer shows a larger partition coefficient, with a $\Delta\Delta G^\circ_{org\rightarrow aq}$ up to 1.4 kcal/mol. A thermodynamic cycle relates these values to a solvent dependence of the *A* value for conformational equilibrium of an amino substituent. The variation with stereoisomer is attributed to a greater hydrophilicity of a cyclohexylamine with an equatorial amino group, or equivalently to a greater steric bulk of an amino group whose lone pair is hydrogen bonded to water. The strong dependence on solvent inferred for A_{NMe_2} was confirmed by direct measurement of conformer populations at low temperature.

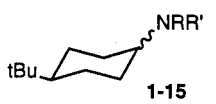
Introduction

***A* Values.** When a bulky substituent on a cyclohexane ring is axial, it suffers repulsive interactions with the axial hydrogens. The free-energy difference between equatorial and axial conformers is a quantitative measure of the size of the substituent, often called the *A* value of that substituent (eq 1).[1] Amino groups are of particular interest as versatile substituents of adjustable bulk and potential hydrogen bonding capability, and the stereodynamics of several tertiary amines have recently been elucidated.[2]

$$A = \Delta G^\circ_{eq\rightarrow ax} = G^\circ_{ax} - G^\circ_{eq} = -RT\ln([ax]/[eq]) > 0 \quad (1)$$

We recently developed a new NMR titration method for highly accurate experimental evaluation of ΔA, the difference between the *A* values of an ionic substituent and its corresponding neutral.[3] This represents a quantitative measure of the steric hindrance to ionic solvation, as expressed by the extra energy to solvate the charge when it is axial.

For various amino substituents it was found that ΔA is >0, corresponding to a hindrance to solvation of an axial cation.[4] However, for some NHR or NR_2 that are especially bulky ΔA is unexpectedly <0. In these cases protonation of the nitrogen increases the proportion of axial conformer. It is unreasonable that the positive charge is better solvated when it is axial. Therefore an alternative explanation is that there is appreciable steric hindrance to solvation of the neutral, even more than of the ion. To test this, we have measured relative partition coefficients of stereoisomeric 4-*tert*-butylcyclohexylamines (**1**−**15**, R, R′ as in Table 1), and we relate these to a solvent dependence of the *A* values of amino groups. Since the solvent dependence is sometimes unusually large, we have confirmed these results by direct measurement of A_{NMe_2} in two slightly different solvents. This methodology permits a novel probe of hydrophobic/hydrophilic interactions, a topic of widespread current interest.[5]



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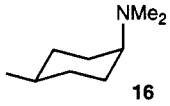

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Experimental Section

Cyclohexylamines. Amines **2**−**5** and **10**−**12** were prepared from 4-*tert*-butylcyclohexanone, the appropriate amine, and formic acid.[6] For **6**−**9**, **14**, and **15** $NaBH_3CN$ was the reductant,[7] and **13** was prepared from commercial 4-*tert*-butylcyclohexylamine (**1**), formaldehyde, and formic acid.[8] The cis/trans mixtures of amine stereoisomers, purified by distillation, were not separated but were characterized by ^1H and ^{13}C NMR,[9] and were used in whatever ratio was obtained. *cis*-*N*,*N*,4-Trimethylcyclohexylamine (**16**) was prepared by hydrogenation of *N*,*N*-dimethyl-*p*-toluidine and separation of the cis isomer by preparative GLC.[10]

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Table 1. Relative Intensities, Partition Coefficient Ratios, and Cis/Trans Solvent Partition Coefficient Free-Energy Differences ($\Delta\Delta G°_{pentane\rightarrow protic}$, kcal/mol) of 4-*tert*-Butylcyclohexyl-NRR′ at 25 °C

	R	R′	I_{cis}^{before}	I_{trans}^{before}	I_{cis}^{after}	I_{trans}^{after}	r	$\Delta\Delta G°$ [a]
1	H	H	0.21	0.79	0.08	0.48	2.44	0.53
2	CH_2CH_3	H	0.35	0.65	0.26	0.57	2.17	0.47
3	$CH_2CH(CH_3)_2$	H	0.28	0.73	0.10	0.46	3.04	0.66
4	$CH_2C(CH_3)_3$	H	0.29	0.72	0.05	0.37	4.56	0.90
5	$CH(CH_3)_2$	H	0.32	0.68	0.17	0.43	1.51	0.24
6	cC_3H_5	H	0.38	0.62	0.13	0.39	3.30	0.71
7	cC_4H_7	H	0.38	0.62	0.16	0.42	3.00	0.65
8	cC_5H_9	H	0.59	0.41	0.20	0.21	1.99	0.41
9	cC_6H_{11}	H	0.51	0.50	0.16	0.21	1.59	0.28
10	CH_2CH_2OH	H	0.27	0.73	0.21	0.59	1.30	0.16
11	$C(CH_3)_3$	H	0.42	0.58	0.06	0.17	2.80	0.61
12	$C(CH_3)_2CH_2OH$	H	0.41	0.59	0.34	0.50	1.11	0.06
13	CH_3	CH_3	0.14	0.86	0.03	0.63	10.9	1.4
14	$-CH_2CH_2CH_2CH_2-$		0.37	0.63	0.17	0.54	6.31	1.09
15	$-CH_2CH_2OCH_2CH_2-$		0.41	0.59	0.25	0.47	2.36	0.51

[a] ±0.07 kcal/mol, from three determinations on each of **1** and **11**.

Spectroscopy. NMR spectra were recorded on a Varian Unity-500 spectrometer (499.8 MHz ^{1}H, 125.7 MHz ^{13}C) with an indirect probe. Chemical shifts are referenced to TMS or 1,4-dioxane. Temperatures were calibrated from the chemical shifts of a separate methanol sample.[11]

Assignments of the H1 signals of the cyclohexyl ring of the cis and trans stereoisomers of **1**−**15** were based on chemical shifts and coupling constants.[12] These characteristic signals are well separated downfield from all others. The axial H1 of a trans stereoisomer is less downfield and shows a large anti coupling, whereas the equatorial H1 of a cis stereoisomer shows only small gauche couplings, which confirm that even for this stereoisomer the *tert*-butyl group is predominantly equatorial.

Partition Coefficient Ratios. The ratios of partition coefficients of cis and trans stereoisomers between pentane and 3:1 CD_3OD/D_2O were determined by extraction and ^{1}H NMR spectroscopy. A solution containing a mixture of the cis and trans stereoisomers (0.050 g), 35% $NaOD/D_2O$ (5 μL), and sodium acetate (0.01 g) as internal standard in 3:1 CD_3OD/D_2O (2.0 mL) was divided into two samples. A ^{1}H NMR spectrum was acquired of the first sample and the integrated area of the H1 signal of each of the stereoisomers was measured, relative to the methyl signal of sodium acetate, and normalized to sum to 1. The second sample was extracted with pentane (ca. 0.2 mL, varying with amine hydrophobicity), and another NMR spectrum acquired of the aqueous layer. The two areas were again measured, relative to acetate methyl. The sodium acetate was assumed not to extract into pentane. The percentage of each stereoisomer remaining in the aqueous layer was determined from the relative intensities in the aqueous layer before and after extraction (eq 2, likewise for % $trans_{aq}$). The percentage of each stereoisomer extracted into the pentane layer was determined by difference (eq 3, likewise for % $trans_p$). The partition coefficient P_{cis} (likewise P_{trans}) is given by eq 4, including the volumes of aqueous and pentane phases. The ratio of partition coefficients r can then be related simply to the percentages (eq 5) inasmuch as the volumes cancel so that they need not be measured.

$$\%\ cis_{aq} = 100\frac{[\text{relative intensity after extraction}]_{aq}}{[\text{relative intensity before extraction}]_{aq}} \quad (2)$$

$$\%\ cis_p = 100 - \%\ cis_{aq} \quad (3)$$

$$P_{cis} = \frac{V_{aq}}{V_p}\frac{\%\ cis_p}{\%\ cis_{aq}} \quad (4)$$

$$r = \frac{P_{cis}}{P_{trans}} = \frac{\%\ cis_p}{\%\ cis_{aq}}\Big/\frac{\%\ trans_p}{\%\ trans_{aq}} \quad (5)$$

Conformational Analysis of *cis*-*N*,*N*,4-Trimethylcyclohexylamine. At −85.6 °C ring inversion of *cis*-*N*,*N*,4-trimethylcyclohexylamine (**16**) is sufficiently slow that its ^{13}C NMR spectrum shows separate, decoalesced signals of the two conformers, one with NMe_2 axial and the other with it equatorial. Downfield C1 (δ 63.8 in CD_2Cl_2) and *N*-methyl (δ 43.5) signals were assigned as axial.[10] The proportions of these conformers in CD_2Cl_2 or in CD_2Cl_2 containing 1% (v/v) CD_3OD were measured by integrating the C1 or *N*-methyl signals under conditions of 0.7-s delay times.

Table 2. Proportion of cis-*N*,*N*,4-Trimethylcyclohexylamine Conformer with NMe_2 Axial at −85.6 °C

solvent	% axial NMe_2[a]	% axial NMe_2[b]	A_{NMe_2}, kcal/mol
CD_2Cl_2	69.0	62.0	1.5
1% $CD_3OD-CD_2Cl_2$	18.2	19.4	2.3

[a] From C1. [b] From *N*-methyls.

Molecular Mechanics Calculations. Energies of axial and equatorial conformers and polar surface areas of *N*-alkylated cyclohexylamines were calculated with MMX (PCMODEL).[13]

Results

The ratios of partition coefficients r (eq 5) of cis and trans stereoisomers between pentane and 3:1 CD_3OD/D_2O were determined by extraction and ^{1}H NMR spectroscopic analysis. The NMR intensities and the ratios are presented in Table 1.

The ratio of partition coefficients can be expressed as a double free-energy difference between stereoisomers and also between solvents (eq 6). These values are included in Table 1. A positive $\Delta\Delta G°$ corresponds to a less favorable partitioning of cis stereoisomer from pentane to protic solvent than for trans. Errors were too large to permit comparison of partition coefficient ratios at 0 and 25 °C, frustrating separation into entropy and enthalpy contributions.

$$RT\ln r = (\Delta G°_{cis})_{org\rightarrow aq} - (\Delta G°_{trans})_{org\rightarrow aq} = \Delta\Delta G°_{org\rightarrow aq} \quad (6)$$

Table 2 lists the proportion of the conformer of *cis*-*N*,*N*,4-trimethylcyclohexylamine with NMe_2 axial at low temperature in both CD_2Cl_2 and CD_2Cl_2 containing 1% CD_3OD. With 10% CD_3OD none of this conformer could be detected. The observed proportions are remarkably sensitive to a small amount of methanol. The same change in relative intensities of the C4-methyls (δ 0.83, 0.77) could be detected in the ^{1}H spectrum, but the peaks were too broad for accurate integration.

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Heats of formation of equatorial conformers of *N*-alkylated cyclohexylamines as calculated by molecular mechanics verify that the equatorial conformer is more stable. The values do not provide much insight into the partition coefficients, which are a solvation phenomenon. More informative are the polar surface areas, which show that the nitrogen lone pair in the axial conformer has a lower accessibility to water, especially for $N(CH_3)_2$.

Discussion

Partition Coefficient Ratios. The intensity data in Table 1 show that the cis stereoisomer of a 4-*tert*-butylcyclohexylamine has a greater tendency to extract from aqueous methanol into pentane. This represents a greater hydrophobicity of the cis, whereas the trans stereoisomer is more hydrophilic. The partition coefficients can differ by more than a factor of 10, quite a large value for molecules that are merely stereoisomers of each other. These results are consistent with the lower water-accessible surface areas in the axial conformers of the cyclohexylamines, which model the cis conformers of the *tert*-butyl-substituted derivatives.

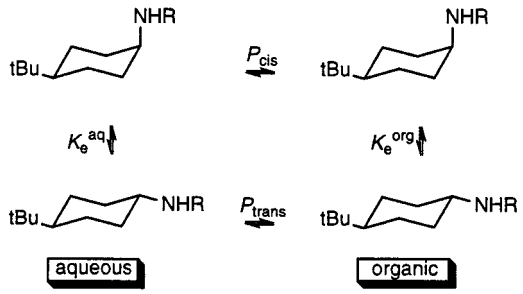
The greater partition coefficient for the cis translates into a positive $\Delta\Delta G°$ (eq 6), ranging from 0.06 to 1.4 kcal/mol. This result is opposite to the partition coefficients of alcohols, where the greater hydrophilicity of the more highly branched isomer is attributed to the need to create a smaller cavity in water.[14] However, the analogy to branching may not apply to the *cis*-4-*tert*-butylcyclohexylamines. Certainly the magnitude of the difference between partition coefficients of these stereoisomers can be quite large, larger than even for structural isomers with the same functional groups.

The partition coefficient $\Delta\Delta G°$s of **2**−**4**, with primary alkyl amino groups $NHCH_2CH_3$, $NHCH_2CH(CH_3)_2$, and $NHCH_2C(CH_3)_3$, increase with β-branching. The high value in this last, nearly 1 kcal/mol, is consistent with severe hindrance to the nitrogen lone pair, as depicted in **17**. Yet increased α-branching, from *N*-ethyl to *N*-isopropyl (**5**) to *N*-*tert*-butyl (**11**), leads to a decrease in $\Delta\Delta G°$, then an increase. It is difficult to assess the hindrance imposed on the lone pair by an α-branch, especially since the conformation about the exocyclic C−N bond is uncertain and may approach an eclipsed one.[15]

The partition coefficient $\Delta\Delta G°$s of the homologous *N*-cycloalkyl-4-*tert*-butylcyclohexylamines **6**−**9** show a monotonic decrease with increasing ring size. The value for the *N*-cyclohexyl derivative **9** is quite similar to that of the *N*-isopropyl derivative **5**. Although the cis stereoisomer is always the more hydrophobic, the relative hydrophobicity decreases with increasing ring size.

The partition coefficient $\Delta\Delta G°$s for tertiary amines **13** and **14**, with dimethylamino and pyrrolidino groups, are the largest among all the amines studied, 1.4 and 1.09 kcal/mol, respectively. They are indicative of quite a large hydrophobicity of the cis stereoisomer. This may be attributed to the inaccessibility of the nitrogen lone pair, which is buried between the axial hydrogens of the cyclohexane. Here there is no ambiguity regarding the conformation about the exocyclic C−N, which must be as in **18**. In contrast, the morpholino derivative **15**, with additional hydrogen-bonding sites, has a lower $\Delta\Delta G°$. Similar reductions are also observed between **2** and **10**, with $NHCH_2CH_3$ and $NHCH_2CH_2OH$ groups, and between **11** and **12**, with $NHC(CH_3)_3$ and $NHC(CH_3)_2CH_2OH$. The additional hydroxyl group reduces the need to solvate the amine in a polar solvent, thereby making the cis and trans stereoisomers more similar in hydrophilicity.

Scheme 1



Relationship between Partition Coefficients and *A* Values. The partition coefficients of the two stereoisomers can be constructed into a thermodynamic cycle, as in Scheme 1. The vertical equilibria cannot be established, since we lack a catalyst that interconverts cis and trans. Yet eq 7 relates the ratio of equilibrium constants to the difference in *A* values of the amino substituent in the two solvents (subject to the assumption that the *tert*-butyl group remains equatorial). It follows from thermodynamics that the ratio $K_{e,aq}/K_{e,org}$ must equal the ratio P_{cis}/P_{trans}, which is thereby also related to the difference in *A* values, as in eq 7. Alternatively, eq 6 can be rearranged to eq 8, and comparison with eq 1 then shows that the $\Delta\Delta G°$ from partition coefficients must also equal the difference in *A* values between the two solvents.

$$RT\ln(K_{e,aq}/K_{e,org}) = A_{aq} - A_{org} = RT\ln(P_{cis}/P_{trans}) \quad (7)$$

$$\Delta G°_{org\rightarrow aq} = (G°_{cis} - G°_{trans})_{aq} - (G°_{cis} - G°_{trans})_{org} = A_{aq} - A_{org} \quad (8)$$

Therefore the $\Delta\Delta G°$s in Table 1 also represent $A_{aq} - A_{org}$, the difference in *A* values between aqueous methanol and pentane. These can be quite large, especially for some dialkylamino groups.

So large a variation does not seem to have been anticipated, but it is quite reasonable. It has been difficult to establish a solvent dependence because many early methods were unreliable and the values were imprecise.[16] Most *A* values, as for the halogens, are simply a measure of size and do not depend strongly on solvent. Small variations are associated with hydrogen bonding, which increases A_{OH} from 0.92 kcal/mol in toluene to 1.04 kcal/mol in methanol. A slightly larger variability was seen for A_{COOEt}.[17] Similarly, from comparisons of chemical shifts, A_{NH_2} seems to increase from 1.15 kcal/mol in non-hydrogen-bonding solvents to 1.45 kcal/mol in hydrogen-bonding ones.[18] This difference was confirmed by that same method,[19] but not by the more reliable integration of peaks at low temperature.[20] We now have conclusive evidence for a large variation of *A* with solvent.

Above, the partition coefficients were interpreted in terms of a greater hydrophobicity of the cis stereoisomers. Alternatively,

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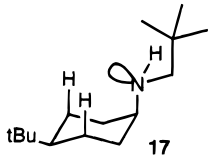
the data can be interpreted in terms of a greater steric bulk of an amino substituent that carries a water molecule hydrogen bonded to the lone pair. For a tertiary amine, with the lone pair as in **18**, the steric repulsion energy becomes quite large. Only in the equatorial conformer is the lone pair adequately accessible to hydrogen bonding with the solvent.



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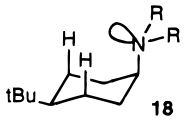

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Variation of A_{NMe_2} with Solvent. The variation of *A* with solvent is inferred indirectly, from partition coefficients. Since this is so much larger than had previously been observed, it is desirable to verify the large value for NMe_2 by a direct method.

The intensity-weighted average axial/equatorial ratios in Table 2, along with the known A_{Me} of 1.74 kcal/mol,[21] can be converted into the *A* value of the dimethylamino group, which is included in Table 2. The value in CD_2Cl_2 agrees fortuitously well with the 1.53 or 1.31 kcal/mol in $CFCl_3-CDCl_3$ or toluene, determined by the same method. The value in 1% methanol agrees well with the 2.1 kcal/mol in 80% methyl Cellosolve, determined by comparison of pK_as, which is dubious.[22] The values in Table 2 show that even a small amount of methanol leads to a large increase in A_{NMe_2}. This is consistent with the partition coefficient $\Delta\Delta G°$ of 1.4 kcal/mol for **13**, since this is equal to the increase of A_{NMe_2} between pentane and 3:1 CD_3OD/D_2O.

Conclusions. The cis isomer of a 4-*tert*-butylcyclohexylamine shows a larger partition coefficient between aqueous methanol and pentane than the trans, sometimes by more than a factor of 10, corresponding to a $\Delta\Delta G°_{org\rightarrow aq}$ up to 1.4 kcal/mol. This is an unusually large difference between stereoisomers. The variation can be attributed to a greater hydrophilicity (hydrophobicity) of a cyclohexylamine with an equatorial (axial) amino group. A thermodynamic cycle relates these values to an unexpectedly large solvent dependence of the *A* value for conformational equilibrium of an amino substituent. This is consistent with a greater steric bulk for an amino group whose lone pair is hydrogen bonded to water, especially for a dialkylamino group, where that lone pair is constrained above the ring in the axial conformer. The large solvent dependence of A_{NMe_2} could be confirmed by direct measurement of conformer populations at low temperature.

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