# Solvation Effect on Steric Bulk of Ionic Substituents: Imidazolium vs Imidazole

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To compare the steric bulk of a cationic substituent with that of the corresponding neutral one, the conformational equilibria of *cis*-*N*-(4-methylcyclohexyl)imidazole (**1-c**), *cis*-*N*-(4-phenylcyclohexyl)-imidazole (**2-c**), and their conjugate acids were measured by low-temperature NMR. The *A* value of an imidazolyl group (equatorial-to-axial free-energy change of *N*-cyclohexylimidazole) is 2.2 ± 0.1 kcal/mol, in both dichloromethane and methanol. The *A* value of an *N*-protonated imidazolyl group in these solvents is 2.2 ± 0.1 kcal/mol. Within the experimental error of this method, the cationic substituent is the same size as the neutral. To measure the relative sizes more precisely, an NMR titration method, applicable to a mixture of isomers, was developed. The ratio of acidity constants of *cis*- and *trans*-*N*-(4-phenylcyclohexyl)imidazoles could be determined from the variation of H1 chemical shifts as a 1:1 mixture was titrated with DCl. In aqueous acetone the *cis* isomer is found to be 0.048 ± 0.002 p*K* unit less basic. This corresponds to a $\Delta A = A_{N\text{-imidazolylH}^+} - A_{N\text{-imidazolyl}}$ of 0.089 ± 0.004 kcal/mol, with the protonated imidazolyl slightly but detectably larger. In $CD_2Cl_2$ the difference is smaller, and in DMSO-$d_6$ it reverses. The significance of this result for the reverse anomeric effect in *N*-glycosylimidazolium ions is discussed.

## Introduction

A monosubstituted cyclohexane exists primarily as that chair conformer with the substituent equatorial. When the substituent is axial, it suffers destabilizing 1,3-diaxial interactions with the axial hydrogens at C3 and C5. The *A* value, or free-energy difference between axial and equatorial conformers, $\Delta G°_{E\to A}$, is a quantitative measure of the effective size of a substituent.[1]

How does solvation of a charged substituent affect its size? There are two conflicting comparisons of corresponding charged and uncharged substituents. One is that of $NH_3^+$ and $NH_2$, where *A* increases by ca. 0.3 kcal/mol upon *N*-protonation.[2] However, part of this increase is due simply to the extra proton of $NH_3^+$, which makes it isosteric to $CH_3$, whereas $NH_2$ may direct its lone pair toward the axial hydrogens and avoid the 1,3-diaxial repulsions. Therefore in this case the influence of cationic solvation must be less than 0.3 kcal/mol. The other comparison is of COOH and $CO_2^-$. According to p$K_a$s of stereoisomeric 4-*tert*-butylcyclohexanecarboxylic acids,[3] $A_{CO_2^-} - A_{COOH}$ is large, 0.7 kcal/mol, even though the lack of a proton might have made the anion smaller. This difference between amino and carboxyl substituents has been confirmed, although it disappears in DMSO.[4]

To compare the steric bulk of a cationic substituent with that of the corresponding neutral one, we would like to focus on the charge effect alone while minimizing the steric effect due to the proton itself. To do so, we need a substituent where the charge is delocalized and where protonation occurs at a more distant atom. Therefore we have chosen to evaluate the *A* values of imidazolyl and of *N*-protonated imidazolyl. To what extent does the necessity for solvation of the charge increase the size of this latter substituent?

This is of particular relevance to the reverse anomeric effect,[5] which has been called into question.[6] Upon *N*-protonation the proportion of axial conformer of *N*-(tetra-*O*-acetyl-α-D-xylopyranosyl)imidazole is claimed to decrease.[7] This was attributed to electronic interactions, since the steric requirement of the imidazolyl substituent was thought not to change on protonation. Yet even though the distant proton itself does not add much bulk, introduction of a positive charge is likely to change the solvation shell about the substituent, and the associated counterion may also influence the equilibrium. Besides, the C1–N bond does shorten. All these effects ought to increase the effective size of the imidazolyl substituent. The assumption that there is no change is therefore worth testing.

Since the relatively large imidazolyl substituent strongly favors the equatorial position, the proportion of axial conformer in cyclohexylimidazole may not be easily or reliably measured. An alternative is to use a *cis*-1,4-disubstituted cyclohexane, since the additional substituent makes the distribution of conformers more balanced.

Therefore we have prepared *cis*-*N*-(4-methylcyclohexyl)imidazole (**1-c**) and *cis*-*N*-(4-phenylcyclohexyl)imidazole (**2-c**) and measured the conformational equilibrium for both, as well as for their *N*-protonated derivatives. Below −80 °C the conformational inversion is slow enough that $^1H$ or $^{13}C$ NMR signals from both chair conformers may be observed. Signals may then be integrated to provide a direct measurement of the position of equilibrium. Since *A* values are frequently solvent dependent,[8] especially for those substituents that can participate in hydrogen bonding, we have investigated

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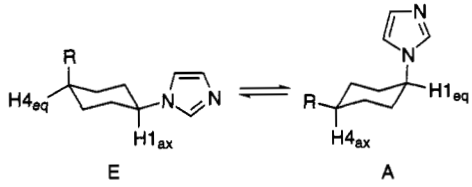
the conformational equilibria in both dichloromethane and methanol. We now report that an *N*-protonated imidazolyl is subject to only slightly larger steric interactions than imidazolyl itself, and we have developed an NMR titration method that provides a precise quantitative measure of the difference.




**1-c**, R = Me
**2-c**, R = Ph

## Experimental Section

**Materials**. 4-Methylcyclohexanone, 4-phenylcyclohexanone, DCl/$D_2O$, methanol-$d_4$, dichloromethane-$d_2$, and other reagents were obtained from commercial suppliers and used as received. Imidazole was recrystallized from ethyl acetate. Dichloromethane was dried by distillation from $CaH_2$ and stored under nitrogen. *p*-Toluenesulfonic acid was dehydrated by azeotropic distillation with benzene. Melting points are uncorrected.

**Mass Spectrometry**. High-resolution mass spectrometry was done on a VG-ZABZFHF or VG-7070EHF mass spectrometer at the University of California, Riverside, Mass Spectrometry facility.

**1-(*N*-Imidazolyl)-4-methylcyclohexene**. Ogata's imidazole transfer reaction,[9] wherein *N,N'*-thionyldiimidazole transfers one or two imidazolyl groups to a ketone, was adapted to favor the transfer of a single imidazole to a substituted cyclohexanone. Dry $CH_2Cl_2$ (ca. 40 mL) was added to 7.93 g of imidazole (116 mmol), and 4.32 g of $SOCl_2$ (36.3 mmol) was added dropwise with stirring and cooling in ice. After ca. 10 min the reaction mixture was added dropwise over ca. 2 h to a solution of 2.18 g of 4-methylcyclohexanone (19.4 mmol) in 30 mL of $CH_2Cl_2$. The mixture was stirred for 3 days, then neutralized with aqueous $NaHCO_3$, extracted with $CH_2Cl_2$, washed, and dried with $Na_2SO_4$. After evaporation of solvent the residue was chromatographed on silica gel and the product was eluted with 2% MeOH in $CH_2Cl_2$. The product (1.22 g, 39%) was used in the following step without further purification. $^1H$ NMR ($CDCl_3$): $\delta$ 1.02 (d, 3H), 1.42 (m, 1H), 1.79 (m, 1H), 1.90 (m, 1H), 2.00 (m, 1H), 2.28 (m, 1H), 2.36 (m, 1H), 2.45 (m, 1H), 5.81 (m, 1H), 7.07 (s, 1H), 7.11 (s, 1H), 7.68 (s, 1H). $^{13}C$ NMR ($CDCl_3$): $\delta$ 20.3, 26.2, 27.3, 29.9, 31.9, 114.8, 115.9, 128.6, 132.7, 133.8. HRMS (70 eV EI) calcd for $C_{10}H_{14}N_2$ ($M^+$) *m/e* 162.1158, found 162.1164.

***N*-(4-Methylcyclohexyl)imidazole (1)**. 1-(*N*-Imidazolyl)-4-methylcyclohexene (50 mg, 0.22 mmol), trifluoroacetic acid (0.1 mL, 1.3 mmol), and 10% Pt/C (100 mg, 0.44 mmol) were mixed in 4 mL of ethanol and mechanically agitated under 45 psi of $H_2$. After 3 days the reaction had gone to completion, as judged by disappearance of the $\delta$ 5.8 peak in the $^1H$ NMR spectrum. Filtration, titration to alkaline pH with 1 M NaOH, extraction into $CH_2Cl_2$, washing, drying, and solvent evaporation produced a 1:1 mixture of *cis*- and *trans*-*N*-(4-methylcyclohexyl)imidazole. NMR experiments were carried out on the mixture. $^1H$ NMR ($CDCl_3$) (1:1 *cis*–*trans* mixture): $\delta$ 0.98 (d, 3H), 1.05 (d, 3H), 1.17 (m, 2H), 1.48 (m, 4H), 1.67 (m, 4H), 1.85 (m, 4H), 2.02 (m, 4H), 3.90 (m, 1H), 4.02 (m, 1H), 6.98 (s, 1H), 7.01 (s, 1H), 7.06 (s, 1H), 7.10 (s, 1H), 7.57 (s, 1H), 7.59 (s, 1H). $^{13}C$ NMR in $CDCl_3$ (**1-c**, assigned from its broadening and resharpening at low temperatures): $\delta$ 18.1, 27.0, 28.1, 29.6, 58.1, 118.9, 120.2, 133.7. (**1-t**): $\delta$ 21.9, 31.1, 33.1, 33.2, 59.2, 119.1, 120.2, 133.8. HRMS (EI 70 eV) calcd for $C_{10}H_{16}N_2$ ($M^+$) *m/e* 164.1315, found 164.1312.

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**Table 1. Relevant $^1H$ Chemical Shifts of *cis*-*N*-(4-R-cyclohexyl)imidazoles 1-c and 2-c**

| R | solvent | $\langle\delta_{H1}\rangle^a$ | $\langle\delta_{H4}\rangle^a$ | $\delta_{H1_{ax}}{}^b$ | $\delta_{H4_{eq}}{}^b$ | $\delta_{H1_{eq}}{}^b$ | $\delta_{H4_{ax}}{}^b$ |
|---|---|---|---|---|---|---|---|
| Me | $CD_2Cl_2$ | 3.98 | 2.08 | 3.84 | *c* | 4.15 | *c* |
| Me | $CD_2Cl_2$/TSA | 4.28 | 2.20 | 4.13 | *c* | 4.37 | *c* |
| Me | $CD_3OD$ | 4.11 | 2.03 | 4.06 | *c* | 4.27 | 2.05 |
| Me | $CD_3OD$/TFA | 4.38 | 2.17 | 4.30 | *c* | 4.48 | *c* |
| Ph | $CD_2Cl_2$ | 4.27 | 2.82 | 4.02 | 3.09 | 4.31 | 2.58 |
| Ph | $CD_2Cl_2$/TFA | 4.52 | 2.92 | 4.33 | 3.18 | 4.55 | 2.67 |
| Ph | $CD_3OD$/TFA | 4.58 | 2.88 | 4.57 | *c* | 4.49 | *c* |

[a] At 27 °C. [b] At −98 or −92 °C. [c] Indeterminate owing to signal overlap.

**1-(*N*-Imidazolyl)-4-phenylcyclohexene**. This was prepared as above but with 4-phenylcyclohexanone (3.38 g, 19.4 mmol) and 3.5 g of $SOCl_2$. The crude product (2.69 g) was chromatographed on silica gel, eluted with 2.5% MeOH in $CH_2Cl_2$, and recrystallized from $CH_2Cl_2$–hexanes as colorless needles (0.96 g, 22%), mp 127–128 °C. $^1H$ NMR ($CDCl_3$): $\delta$ 2.04 (1H, m), 2.21 (1H, m), 2.43 (1H, m), 2.60 (2H, m), 2.66 (1H, m), 2.99 (1H, m), 5.60 (1H, m), 7.19 (1H, m), 7.21 (1H, s), 7.30 (3H, m), 7.41 (2H, m), 7.81 (1H, s). $^{13}C$ NMR: $\delta$ 27.7, 29.4, 32.0, 39.3, 115.6, 116.6, 126.5, 126.7, 128.6, 129.4, 133.5, 134.4, 145.3. HRMS (EI 70 eV) calcd $C_{15}H_{16}N_2$ ($M^+$) *m/e* 224.1315, found 224.1312.

***N*-(4-Phenylcyclohexyl)imidazole (2)**. 1-(*N*-Imidazolyl)-4-phenylcyclohexene (0.5 g, 2.23 mmol), trifluoroacetic acid (1 mL, 13 mmol), and platinum oxide (100 mg, 0.44 mmol) were mixed in 10 mL of methanol and mechanically agitated under 45 psi of $H_2$. After 3 days the reaction mixture was filtered and the solvent was removed under vacuum. The solution was neutralized with 1 N NaOH and extracted into $CH_2Cl_2$. A 1:1 mixture of the *cis* and *trans* isomers of *N*-(4-phenylcyclohexyl)-imidazole (0.46 g, 91%) was obtained upon solvent evaporation. Alternatively, hydrogenation in the absence of trifluoroacetic acid provided a 3:1 mixture of *cis* and *trans* isomers, along with 50% starting material. Separation of these three components could be accomplished by HPLC elution with 0.8% MeOH in $CH_2Cl_2$ on a silica gel column. The $^1H$ and $^{13}C$ signals of the first band broaden and resharpen at low temperature, so this was assigned as the *cis* isomer, **2-c**. $^1H$ NMR (acetone-$d_6$): $\delta$ 1.83 (m, 4H, H3,5), 2.06 (m, 2H, $H2,6_{ax}$), 2.29 (m, 2H, $H2,6_{eq}$), 2.83 (m, 1H, H4), 4.36 (m, 1H, H1), 6.93 (s, 1H, $H_{Im}$), 7.18 (m, 2H, $H_{Ph}$), 7.27 (m, 4H, $H_{Ph,Im}$), 7.68 (s, 1H, $H_{Im2}$). $^{13}C$ NMR (acetone-$d_6$): $\delta$ 29.3, 33.8, 41.8, 53.1, 117.7, 126.7, 127.5, 129.2, 129.4, 136.23, 146.7. The remaining peaks were assigned to the *trans* isomer, **2-t**. $^1H$ NMR (acetone-$d_6$): $\delta$ 1.72 (m, 2H, $H3,5_{ax}$), 1.93 (m, 2H, $H2,6_{ax}$), 2.00 (m, 2H, $H3,5_{eq}$), 2.18 (m, 2H, $H2,6_{eq}$), 2.68 (m, 1H, H4), 4.21 (m, 1H, H1), 6.90 (s, 1H, $H_{Im}$), 7.17 (m, 2H, $H_{Ph}$), 7.26 (m, 4H, $H_{Ph,Im}$), 7.61 (s, 1H, $H_{Im2}$). $^{13}C$ NMR (acetone-$d_6$): $\delta$ 30.9, 35.0, 43.9, 56.6, 118.4, 126.9, 127.7, 129.2, 129.5, 136.7, 147.3. HRMS (EI 70 eV) calcd for $C_{15}H_{18}N_2$ ($M^+$) *m/e* 226.1471, found 226.1470.

**NMR Spectrometry**. Spectra were recorded on a GE QE-300 spectrometer (300 MHz $^1H$, 75 MHz $^{13}C$) or a Varian Unity-500 spectrometer (499.8 MHz $^1H$, 125.7 MHz $^{13}C$). Chemical shifts are referenced to a solvent signal or other internal standard ($CDCl_3$: residual $^1H$ $\delta$ 7.26, $^{13}C$ $\delta$ 77.0. Dichloromethane-$d_2$: residual $^1H$ $\delta$ 5.32, $^{13}C$ $\delta$ 53.8. Methanol-$d_4$: residual $^1H$ $\delta$ 3.30, $^{13}C$ $\delta$ 49.0. Acetone-$d_6$: residual $^1H$ $\delta$ 2.04, $^{13}C$ $\delta$ 29.8. Homonuclear decoupling experiments, starting from H1 of *N*-(4-phenylcyclohexyl)imidazole, served to assign other $^1H$ NMR signals around the cyclohexane ring. Temperatures were calibrated with a separate 50/50 methanol/methanol-$d_4$ sample.[10] For reliable $^{13}C$ integrations, an interpulse delay of 10 s was used.

Samples were 0.3–0.4 M, except for the *cis*-*N*-(4-phenylcyclohexyl)imidazole isolated by HPLC, which was 0.02–0.04 M. The *N*-protonated derivatives were prepared by further addition of at least 1 equiv of trifluoroacetic acid (TFA) or *p*-toluenesulfonic acid (TSA).

Relative proportions of **A** and **E** conformers were measured by integration of representative $^1H$ or $^{13}C$ signals at low

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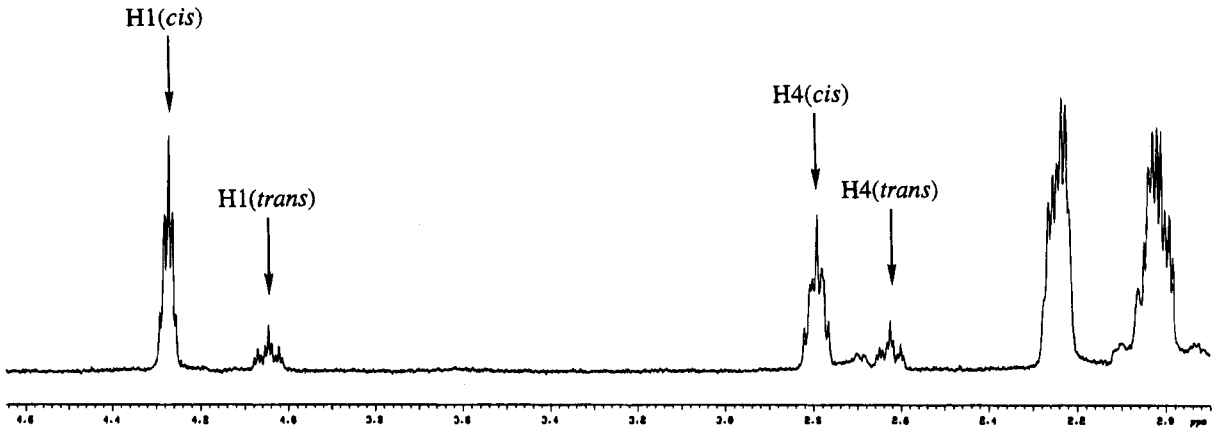



**Figure 1.** $^1$H NMR of *cis*-*N*-(4-phenylcyclohexyl)imidazole (**2-c**) in dichloromethane-$d_2$ at 27 °C.

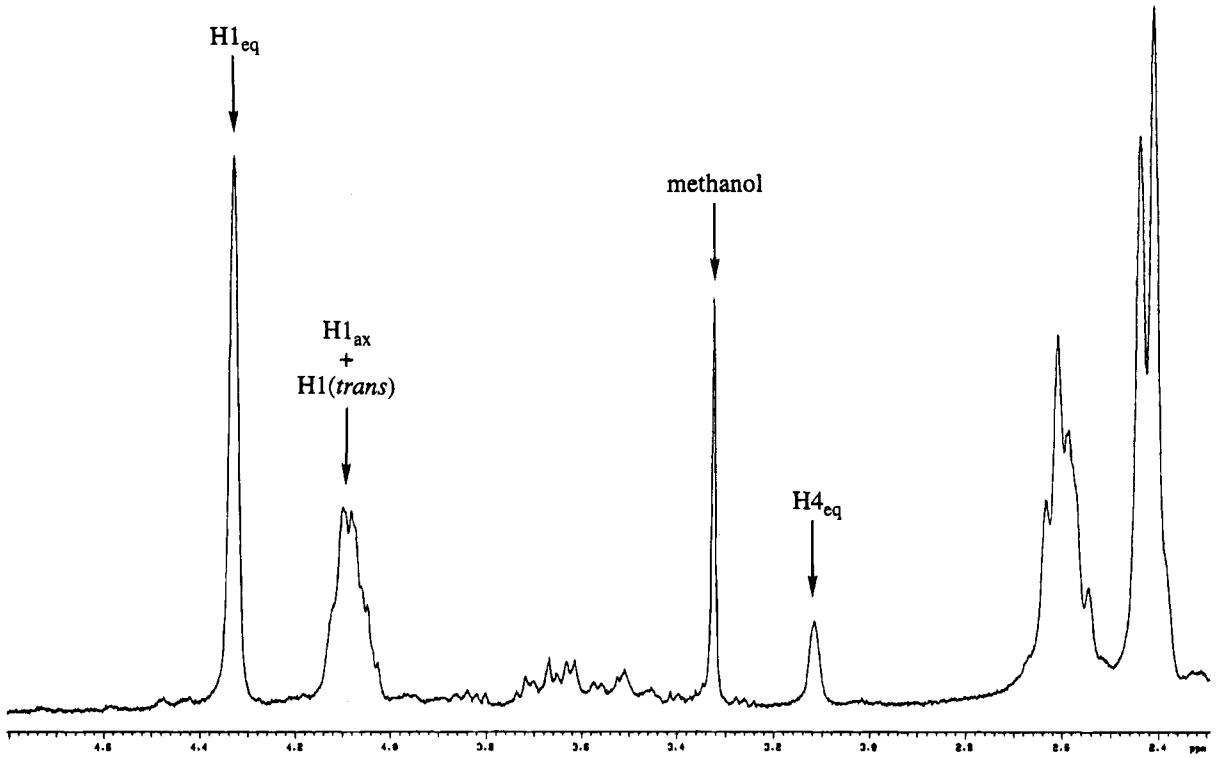
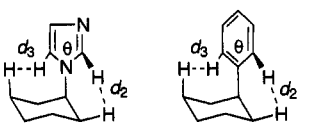



**Figure 2.** $^1$H NMR of *cis*-*N*-(4-phenylcyclohexyl)imidazole (**2-c**) in dichloromethane-$d_2$ at −98 °C.

temperature. In both **1-c** and **2-c** the $^1$H signal from H1 of conformer **E** (designated as $H1_{ax}$) coincides with that of the contaminating *trans* isomer, where H1 is exclusively axial. The proportion of conformer **E** was therefore determined by subtracting from this composite signal the contribution from H1(*trans*), as determined at room temperature, where there is no overlap. This intensity was compared with that of $H1_{eq}$, as a measure of the proportion of conformer **A**. For **2-c** it was also possible to integrate $H4_{eq}$ of **2-cE** and compare this with $H1_{eq}$ of **2-cA**. For **1-c** $^{13}$C NMR was also used. Both the $CH_3$ and C1 signals were integrated, since these are isolated in the spectrum and easily identified. Errors were calculated as standard deviations of at least three measurements on each of two or more samples. The ratio of conformers was converted to a free-energy difference according to $\Delta G°_{E\rightarrow A} = -RT \ln([A]/[E])$.

**Titration of Isomeric Mixture of *N*-(4-Phenylcyclohexyl)imidazole.** To the 1:1 mixture of *cis*- and *trans*-*N*-(4-phenylcyclohexyl)imidazoles (51.4 mg, 0.227 mmol), dissolved in 1.0 mL of 1:1 (v/v) acetone-$d_6$/$D_2O$ containing 0.5% *tert*-butyl alcohol ($\delta$ 1.17) or tetramethylsilane as internal standard, small portions (3 or 5 $\mu$L) of 3.0 N DCl in 1:1 acetone-$d_6$/$D_2O$ were added. The 500-MHz $^1$H NMR chemical shifts of H1 in both isomers at 24.5 °C were recorded after each addition. These same titrations were also performed in $CD_2Cl_2$ and in DMSO-$d_6$.

**Molecular Mechanics Calculations.** Critical distances in the minimum-energy axial conformers of *N*-(cyclohexyl)-imidazole (**3**) and phenylcyclohexane (**4**) were calculated with MMX (PCMODEL).[11] The relative energies of axial and equatorial conformers of **3** and its protonated forms were calculated with MMX and also with AM1 semiempirical molecular orbital theory (MOPAC).[12]

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(11) Serena Software, Box 3076, Bloomington, IN 47402.
(12) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902. Stewart, J. J. P. *QCPE Bull.* **1983**, *3*, 101.

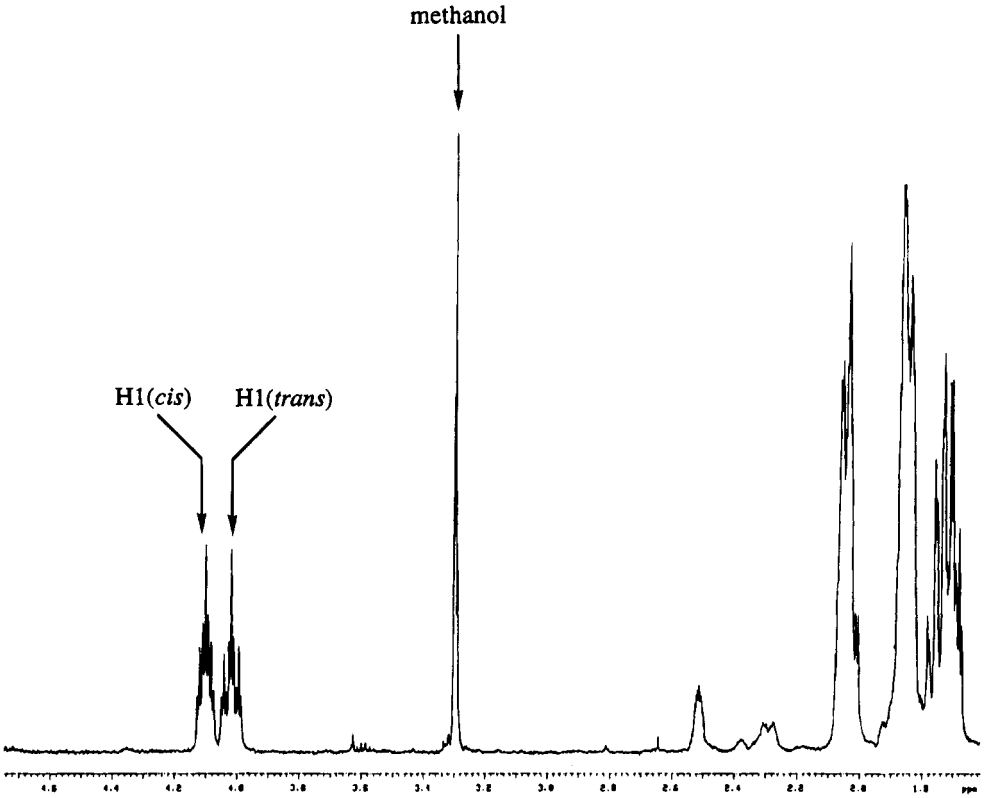


**Figure 3.** $^1$H NMR of *cis-N*-(4-methylcyclohexyl)imidazole (**1-c**) in methanol-$d_4$ at 27 °C.

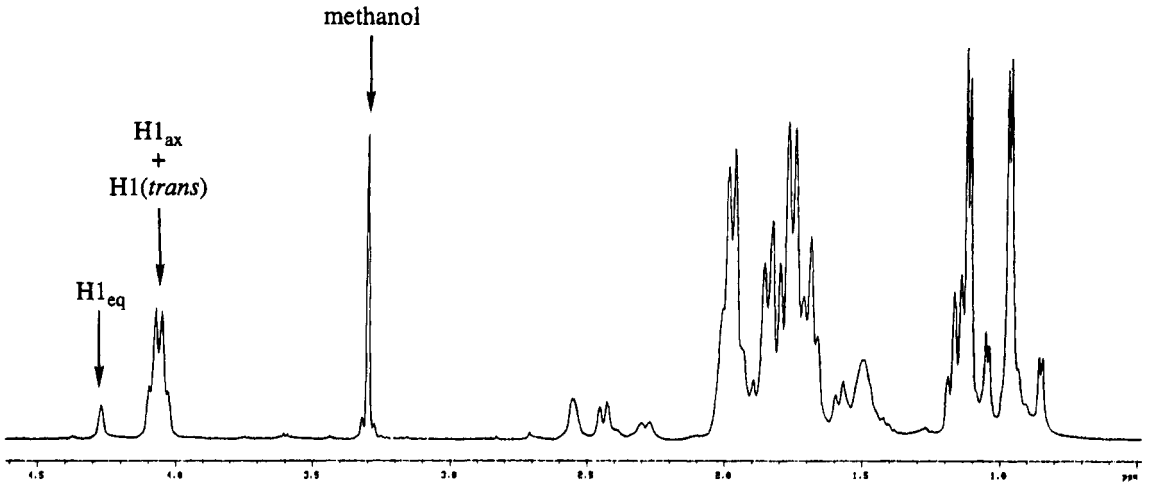


**Figure 4.** $^1$H NMR of *cis-N*-(4-methylcyclohexyl)imidazole (**1-c**) in methanol-$d_4$ at −92 °C.

## Results

***cis-N*-(4-Phenylcyclohexyl)imidazole (2).** The relevant region of the room-temperature $^1$H NMR spectrum of **2** is shown in Figure 1. This was easier to interpret than that of **1** because it was primarily one isomer, although signals from the *trans* isomer **2-t** are apparent, since HPLC purification was not complete. Both H1 and H4 display characteristic downfield signals. Since the chemical shift of *N*-methylimidazole is $\delta$ 3.7,[13] downfield of toluene at $\delta$ 2.3, the multiplets at $\delta$ 4.3 and $\delta$ 2.6 could be assigned as H1 and H4, respectively. Table 1 lists $^1$H chemical shifts in diverse solvents, including acidic media. At room temperature these are averaged chemical shifts of the two conformers.

As the temperature is lowered, the H1 and H4 signals broaden and then each decoalesces into two signals with different intensities. The major isomer has its H1 signal downfield of that of the minor isomer, and its H4 signal upfield. Figure 2 shows the $^1$H NMR spectrum of **2** at −98 °C. Since axial protons in cyclohexane systems are with rare exception upfield of their equatorial counterparts,[14] the major isomer can be identified as **2-cA**, with imidazolyl axial and phenyl equatorial.

***cis-N*-(4-Methylcyclohexyl)imidazole (1).** The $^1$H NMR spectrum of **1** is very similar to that of **2**. The key feature is the H1 signal, near $\delta$ 4. The H4 signals overlap with the other signals and were not used in the analysis. The room-temperature $^1$H spectrum of **1** is shown in Figure 3, and its low-temperature spectrum in Figure 4. Table 1 includes chemical shifts for **1-c** in diverse solvents, including acidic media.

(13) Pouchert, C. J. *Aldrich Library of NMR Spectra, 2nd ed.*; 1983, Vol. 2, 485A.

(14) Jackman, L. M.; Sternhell, S. *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*, 2nd ed.; Pergamon Press: Oxford, 1969; p 238.

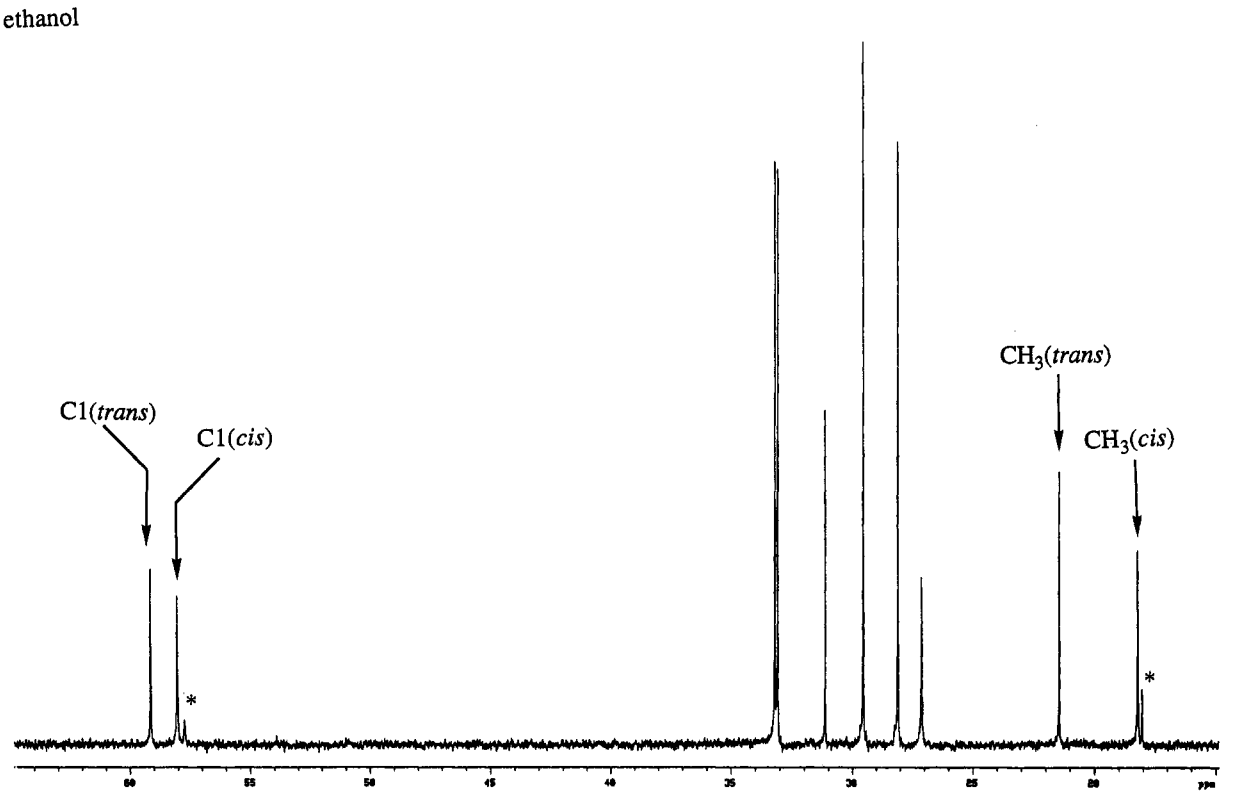


**Figure 5.** $^{13}C$ NMR of *cis-N*-(4-methylcyclohexyl)imidazole (**1-c**) in chloroform-*d* at 27 °C.

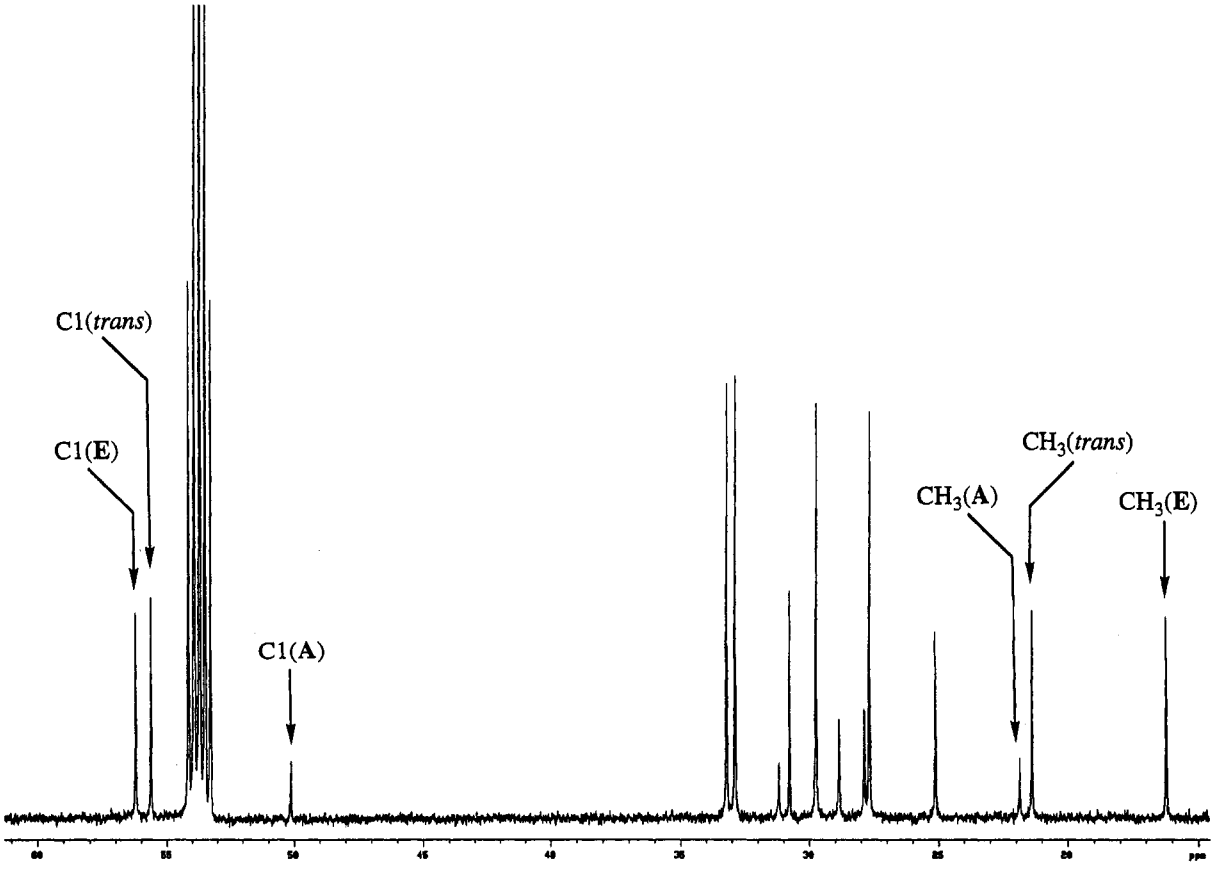


**Figure 6.** $^{13}C$ NMR of *cis-N*-(4-methylcyclohexyl)imidazole (**1-c**) in dichloromethane-$d_2$ at −82 °C.

The conformational equilibrium of **1-c** was also investigated by $^{13}C$ NMR spectroscopy. Since the $^{13}C$ spectra were readily interpreted, separation of the isomers by HPLC was not necessary. The room- and low-temperature $^{13}C$ spectra of a 1:1 mixture of **1-c** and **1-t** are shown in Figures 5 and 6, respectively. Signals from the two isomers were easily distinguished from one another and assigned. As the temperature was lowered, the only signals that broadened and then resharpened were assigned to the *cis* isomer. Besides, since axial substitu-

**Table 2. Relevant $^{13}C$ Chemical Shifts of *cis*-*N*-(4-Methylcyclohexyl)imidazole (1-c)[a]**

| solvent | $\langle\delta_{CH_3}\rangle$ | $\langle\delta_{C1}\rangle$ | $\delta_{CH_3E}$[b] | $\delta_{C1E}$[b] | $\delta_{CH_3A}$[b] | $\delta_{C1A}$[b] |
|---|---|---|---|---|---|---|
| $CD_2Cl_2$ | 17.9 | 55.6 | 16.3 | 56.3 | 21.9 | 50.2 |
| $CD_2Cl_2$/TSA | 18.7 | 56.4 | 16.6 | 59.0 | 22.5 | 52.7 |
| $CD_3OD$ | 19.1 | 56.9 | 17.4 | 58.4 | 23.2 | 52.3 |
| $CD_3OD$/TSA | 18.8 | 60.0 | 17.2 | 60.9 | 23.0 | 55.4 |

[a] ±0.2 ppm. [b] At −82 or −87 °C.

ents generally shift $^{13}C$ signals upfield,[15] assignment of the *trans* isomer **1-t**, with both its substituents equatorial, could be confirmed as the one whose signals are systematically downfield. The relevant $^{13}C$ chemical shifts of the *cis* isomer **1-c** are listed in Table 2. Also included are the shifts of the **A** and **E** conformers at low temperature.

As seen in Figures 4 and 6, decoalescence is complete at these low temperatures. In contrast to the 4-phenyl derivative, H1 of the major isomer is upfield of H1 of the minor isomer, and H4 is downfield. Therefore for **1-c** conformer **E**, with imidazolyl equatorial and methyl axial, is favored.

**Integration.** Table 3 contains the percentage of conformer **A** for both **1-c** and **2-c** in each of the solvent systems studied. Included are the signals that were integrated to evaluate the proportion of each conformer. Equilibrium constants from different reporter nuclei agree within experimental error, but $^{13}C$ results for **1-c** and $^{1}H$ results for **2-c** are judged to be more accurate.

**Titration.** Table 4 lists the $^{1}H$ chemical shifts of H1 in the 1:1 mixture of *cis*- and *trans*-*N*-(4-phenylcyclohexyl)imidazoles, following each addition of DCl. Addition of further DCl did not change the chemical shifts further.

## Discussion

**Conformational Free-Energy Differences.** Although **1-c** exists predominantly as conformer **E**, **2-c** exists primarily as conformer **A**. Therefore the imidazolyl substituent is larger than a methyl but smaller than a phenyl. The free-energy differences, $\Delta G°_{E\rightarrow A}$, between equatorial and axial conformers of cyclohexanes **1-c** and **2-c** are listed in Table 5.

**Molecular Mechanics Calculations.** That imidazolyl is larger than methyl is not surprising. However, the observation that phenyl is larger still is perhaps surprising inasmuch as the shorter C1−N and $N-C_{ring}$ bonds in an *N*-imidazolylcyclohexane ought to increase the steric repulsions between ortho hydrogens on the substituent and hydrogens at C2,6 or C3,5 of the cyclohexane. On the other hand, the C−N−C angle in the five-membered ring is smaller than the ipso C−C−C angle of the phenyl. Molecular mechanics calculations were undertaken to gauge the net effect of these geometrical differences on the repulsions.

MMX calculations on the minimum-energy axial conformer of *N*-(cyclohexyl)imidazole (**3**) provide the bond angle $\theta = 107.2°$, H−H distances $d_2 = 2.29$ Å and $d_3 = 2.42$ Å, and C1−N distance 1.46 Å. For comparison, those values in phenylcyclohexane (**4**) are 118.5°, 2.24 Å, 2.25 Å, and 1.52 Å (C1−$C_{ipso}$), respectively. As has been noted before,[16] the critical repulsion is with the equatorial hydrogen on C2. Thus the distance between the ortho hydrogen and $H2_{eq}$ of the cyclohexane ring is shorter in the phenyl compound than in the imidazolyl compound because the smaller C−N−C angle is more important than the shorter C−N bonds. The shorter H−H distance is responsible for the greater steric destabilization of an axial phenyl than of an axial imidazolyl.

**A values.** Since *A* values are additive,[17] eq 1 relates the free-energy differences in Table 5 to *A* values. The

$$\Delta G°_{E\rightarrow A} = A_{N\text{-imidazolyl}} - A_R \qquad (1)$$

*A* values of the imidazolyl group and of its *N*-protonated form can therefore be calculated using the known[17,18] $A_{Me}$ of 1.74 ± 0.07 kcal/mol and $A_{Ph}$ of 2.9 ± 0.1 kcal/mol. Included in Table 5 are these *A* values for an imidazolyl group. The average *A* value is 2.2 ± 0.1 kcal/mol. The two independent determinations from **1-c** and **2-c** agree quite well with each other. This agreement corroborates the value of $A_{Ph}$. Alternatively, the imidazolyl group may be used as a relay from methyl to phenyl to evaluate $A_{Ph}$ as 2.9 kcal/mol, which agrees exactly with the previous value.

The *A* value of the imidazolyl group displays no detectable dependence on whether the solvent is dichloromethane or methanol. This is not surprising in that only compact substituents that are capable of hydrogen bonding show significant solvent dependence of *A* values.[1,2,19] The imidazolyl substituent is large enough and diffuse enough that its solvation shell apparently does not vary much near the cyclohexane hydrogens with which it interacts.

Within experimental error the *A* value of protonated imidazolyl is also 2.2 ± 0.1 kcal/mol, regardless of solvent or counterion. More remarkably, there is no detectable increase in $A_{N\text{-imidazolyl}}$ upon *N*-protonation. However, it must be admitted that the experimental error is a substantial 0.1 kcal/mol.

**Steric Difference between Imidazolyl and Protonated Imidazolyl.** The absence of any detectable change in $A_{N\text{-imidazolyl}}$ upon *N*-protonation may be merely a consequence of the substantial experimental error. To measure the change more accurately, a 1:1 mixture of *cis*- and *trans*-*N*-(4-phenylcyclohexyl)imidazoles was subjected to an NMR titration with DCl. According to the data in Table 1, the $^{1}H$ chemical shifts of H1 undergo sufficient change on *N*-protonation to permit NMR determination of the extent of protonation. If one isomer is more basic than the other, then during a titration its spectral characteristics will change earlier than those of the other isomer.

What is readily measurable is the ratio of acidity constants of *cis*- and *trans*-*N*-(4-phenylcyclohexyl)imidazoles, called *K* in eq 2. The observed chemical shift of

$$K = \frac{K_a^{CH^+}}{K_a^{TH^+}} = \frac{[C][TH^+]}{[CH^+][T]} \qquad (2)$$

the *cis* isomer **2-c** is given by eq 3, where $\delta_{CH^+}$ and $\delta_C$ are limiting chemical shifts of protonated and unprotonated forms, respectively. A similar equation holds for

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**Table 3. Percent of Conformer A in *cis*-*N*-(4-R-cyclohexyl)imidazoles 1-c and 2-c**

| | | $^1$H NMR | | | $^{13}$C NMR | | |
|---|---|---|---|---|---|---|---|
| R | solvent | $T$, °C | $H1_{eq}$:$H4_{eq}$ | $H1_{eq}$:$H1_{ax}$[a] | $T$, °C | C1**A**:C1**E** | $CH_3$**A**:$CH_3$**E** |
| Ph | $CD_2Cl_2$ | −98 | 87.5 ± 2 | 89 ± 1.5 | | *b* | *b* |
| Ph | $CD_2Cl_2$/TFA | −98 | 83 ± 1 | 83 ± 2 | | *b* | *b* |
| Me | $CD_2Cl_2$ | −92 | *c* | 20 ± 1 | −82 | 24 ± 3 | 25.5 ± 5 |
| Me | $CD_2Cl_2$/TSA | −92 | *c* | 23 ± 3.5 | −82 | 27 ± 3 | 29 ± 4 |
| Me | $CD_3OD$ | −92 | *c* | 22 ± 2 | −87 | 22 ± 2 | 25 ± 3 |
| Me | $CD_3OD$/TFA | −92 | *c* | 23 ± 2 | −87 | 20 ± 2.5 | 20 ± 1 |

[a] Corrected for H1 (*trans*). [b] Not determined. [c] $H4_{eq}$ not resolvable.

**Table 4. $^1$H NMR Chemical Shifts[a] of *N*-(4-Phenylcyclohexyl)imidazole 2 Following Addition of *N* 3-μL Portions of DCl**

| *N* | $\delta_{cis\text{-}H1}$ | $\delta_{trans\text{-}H1}$ | *N* | $\delta_{cis\text{-}H1}$ | $\delta_{trans\text{-}H1}$ | *N* | $\delta_{cis\text{-}H1}$ | $\delta_{trans\text{-}H1}$ |
|---|---|---|---|---|---|---|---|---|
| 0 | 4.263 | 4.070 | 9 | 4.373 | 4.202 | 18 | 4.523 | 4.369 |
| 2 | 4.269 | 4.076 | 10 | 4.382 | 4.212 | 19 | 4.547 | 4.395 |
| 2 | 4.284 | 4.095 | 11 | 4.401 | 4.234 | 20 | *b* | 4.408 |
| 3 | 4.288 | 4.100 | 12 | 4.412 | 4.246 | 21 | *b* | 4.419 |
| 4 | 4.304 | 4.119 | 13 | 4.422 | 4.257 | 22 | *b* | 4.432 |
| 5 | 4.325 | 4.143 | 14 | 4.452 | 4.292 | 23 | 4.580 | 4.429 |
| 6 | 4.341 | 4.163 | 15 | 4.469 | 4.311 | 24 | 4.598 | 4.446 |
| 7 | 4.357 | 4.182 | 16 | 4.487 | 4.330 | 25 | 4.627 | 4.476 |
| 8 | 4.366 | 4.192 | 17 | 4.507 | 4.349 | 26 | 4.632 | 4.481 |

[a] *tert*-Butyl alcohol internal standard. [b] Interference from HOD peak.

**Table 5. $\Delta G°_{E\to A}$, kcal/mol, for *cis*-*N*-(4-R-cyclohexyl)imidazoles**

| R | solvent | $T$, °C | $\Delta G°$ | $A_{N\text{-}imidazolyl}$ |
|---|---|---|---|---|
| Me | $CD_2Cl_2$ | −82 | 0.44 ± 0.06[a] | 2.2 ± 0.1 |
| Me | $CD_2Cl_2$/TSA | −82 | 0.38 ± 0.06[a] | 2.1 ± 0.1 |
| Me | $CD_3OD$ | −87 | 0.47 ± 0.04[a] | 2.2 ± 0.1 |
| Me | $CD_3OD$/TFA | −87 | 0.51 ± 0.02[b] | 2.25 ± 0.1 |
| Ph | $CD_2Cl_2$ | −98 | −0.68 ± 0.06[c] | 2.2 ± 0.1 |
| Ph | $CD_2Cl_2$/TFA | −98 | −0.55 ± 0.02[c] | 2.3 ± 0.1 |

[a] From integration of $^{13}$C1 signals. [b] From integration of $^{13}CH_3$ signals. [c] From integration of $^1H1_{eq}$ of conformer **A** and $H4_{eq}$ of conformer **E**.

$$\delta_c = \frac{\delta_C[C] + \delta_{CH^+}[CH^+]}{[C] + [CH^+]} \quad (3)$$

$\delta_t$, the chemical shift of the *trans* isomer, **2-t**. According to the data in Table 4, the H1 limiting shifts $\delta_{CH^+}$, $\delta_C$, $\delta_{TH^+}$, and $\delta_T$ are 4.632, 4.263, 4.481, and 4.070 ppm, respectively. Algebraic manipulations of eq 2, eq 3, and the equivalent equation for $\delta_t$ lead to eq 4, which is

$$\delta_c = \delta_C + \frac{(\delta_{CH^+} - \delta_C)(\delta_t - \delta_T)}{(1 - K)(\delta_t - \delta_T) + K(\delta_{TH^+} - \delta_T)} \quad (4)$$

nonlinear whenever $K \neq 1$. Indeed, a plot of $\delta_c$ against $\delta_t$ shows slight but systematic upward curvature, indicating that the *trans* isomer is more readily protonated. However, this nonlinear equation is difficult to fit. Alternative manipulations lead to the linearized form in eq 5, relating observed chemical shifts to the desired $K$.

$$(\delta_t - \delta_T)(\delta_{CH^+} - \delta_c) = K(\delta_c - \delta_C)(\delta_{TH^+} - \delta_t) \quad (5)$$

In particular, a plot of $(\delta_t - \delta_T)(\delta_{CH^+} - \delta_c)$ vs $(\delta_c - \delta_C)(\delta_{TH^+} - \delta_t)$ ought to be a straight line, with slope $K$ and zero intercept. (This may be a well-known equation for evaluating a ratio of acidity constants, but it was easier to derive it than to find it in the chemical literature. The closest method of which we are aware is the NMR determination of isotope effects on acidity constants,[20] but this requires accurate aliquots or pH measurement and a nonlinear fit.)

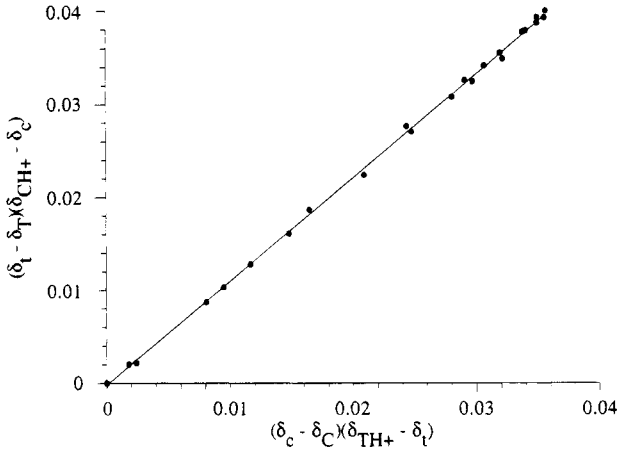


**Figure 7.** Linearized plot of chemical shifts, $(\delta_t - \delta_T)(\delta_{CH^+} - \delta_c)$ vs $(\delta_c - \delta_C)(\delta_{TH^+} - \delta_t)$, during titration of 1:1 mixture of *cis*- and *trans*-*N*-(4-phenylcyclohexyl)imidazoles with DCl in 1:1 acetone-$d_6$/$D_2O$.

**Scheme 1. Acid Dissociation of *cis*-*N*-(4-Phenylcyclohexyl)imidazolium Ion**

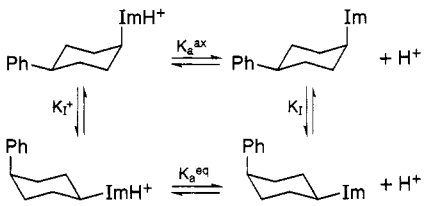


Figure 7 shows such a plot, with chemical shifts from Table 4. The excellent linearity is confirmed by a correlation coefficient of 0.99965. The slope is 1.114 ± 0.006, and the intercept is −0.0002 ± 0.0002, which is properly zero within acceptably small experimental error. A five-parameter nonlinear least-squares fitting of these data to eq 4 gave this same value for $K$. This slope corresponds to a $\Delta pK_a = -\log(K_a^{CH^+}/K_a^{TH^+})$ of −0.048 ± 0.002. A repeat titration using TMS as internal standard gave the same slope, 1.122 ± 0.009. The average is 1.118 ± 0.005. In $CD_2Cl_2$ and DMSO-$d_6$ these slopes are 1.03 ± 0.02 and 0.89 ± 0.01, respectively. It is remarkable that this ratio of acidity constants can be measured with such precision, higher than the acidity constants themselves.

Scheme 1 shows the acid dissociation of *cis*-*N*-(4-phenylcyclohexyl)imidazolium ion, where $K_a^{ax}$ and $K_a^{eq}$

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are the microscopic acidity constants of the conformers with the imidazolium group axial and equatorial, respectively. What we want is $\Delta A$, the difference in $A$ values between protonated and unprotonated imidazolyl groups. This is given in eq 6, where $K_I^+$ and $K_I$ are the equilib-

$$\Delta A = A_{N\text{-imidazolylH}^+} - A_{\text{N-imidazolyl}} = RT \ln(K_I^+/K_I) \quad (6)$$

rium constants, [equatorial imidazole]/[axial imidazole], for ring inversion of the protonated and unprotonated forms, respectively. This equation simplifies because $A_{Ph}$ from eq 1 cancels.

It follows from thermodynamics that the desired ratio $K_I^+/K_I$ must equal $K_a^{ax}/K_a^{eq}$. However, this ratio is not directly measurable; only the ratio in eq 2 is measurable. The macroscopic acidity constant $K_a^{CH^+}$ is related to the microscopic constant by eq 7. For comparison, $K_a^{TH^+}$ of

$$K_a^{CH^+} = \frac{[H^+]\{[ax]+[eq]\}}{[axH^+]+[eqH^+]} = \frac{K_a^{ax} + K_I^+ K_a^{eq}}{1 + K_I^+} \quad (7)$$

the *trans* stereoisomer **2-t** is a good estimate for $K_a^{eq}$, since this stereoisomer has its imidazolyl group exclusively (>99.9%) equatorial. With this substitution, eqs 2 and 7 lead to eq 8, giving the desired ratio. From

$$\frac{K_I^+}{K_I} = \frac{K_a^{ax}}{K_a^{eq}} = \frac{K}{1 - (K-1)K_I} \quad (8)$$

$\Delta G°_{E\to A}$ in Table 5, $K_I$, extrapolated to 25 °C, is 0.32 ± 0.03. Then with the above $K$, eq 8 gives $K_I^+/K_I$ or $K_a^{ax}/K_a^{eq}$ as 1.161 ± 0.008, corresponding to a $\Delta pK_a$ of −0.065 ± 0.003. The extrapolation assumes $\Delta S°_{E\to A} = 0$, but $K_I$ enters into eq 8 only as a small correction. Then from eq 6, $\Delta A$ is 0.089 ± 0.004 kcal/mol, where the error is calculated from the propagation of errors in the various measured values.

This result means that the repulsion energy of a protonated imidazolyl substituent in the axial position of a cyclohexane is detectably greater than that of the unprotonated. This is an effect solely due to the positive charge, since the site of protonation of an *N*-cyclohexylimidazole is remote from the hydrogens on the cyclohexane. The size of the imidazolyl substituent does not change, but its effective size does, through the change of the solvation shell and perhaps through the decrease of the C1−N bond length.

This change in effective size is genuinely an effect of solvation, since in nonaqueous solvents the change is different. In $CD_2Cl_2$ and DMSO-$d_6$ the above values for $K$ lead to $\Delta A$ of 0.024 ± 0.013 and −0.089 ± 0.009 kcal/mol, respectively. In $CD_2Cl_2$ the effect diminishes, and in DMSO-$d_6$ it reverses, with the protonated imidazolyl more stable in the axial position than is the unprotonated.

The change in effective size on *N*-protonation of the imidazolyl substituent is not large. This result is reasonable since even $A_{NH_2}$ increases by only 0.3 kcal/mol upon *N*-protonation.[2] Since the site of protonation of an *N*-cyclohexylimidazole is more remote, the increase of $A_{N\text{-imidazolyl}}$ upon *N*-protonation must be smaller. It is remarkable that this small increase can be measured with such high precision.

The proportion of the axial conformer of *N*-(glucopyranosyl)imidazoles was claimed to decrease upon *N*-protonation.[5,7] We now see that this so-called reverse anomeric effect cannot be attributed merely to an increased steric bulk of the substituent, inasmuch as $A_{N\text{-imidazolyl}}$ hardly increases upon *N*-protonation. As suggested by Paulsen and Lemieux, there are indeed no large solvation effects on the conformational equilibrium of imidazole derivatives. Nevertheless, although the reverse anomeric effect was attributed to electronic interactions, we have recently found[6] that there is no such effect in glucopyranosylamines.

The change in effective size due to protonation can be evaluated accurately by this NMR titration method. The difference in $pK_a$ between axial and equatorial groups can be measured without using the monosubstituted *N*-cyclohexylimidazole, without equilibrating the *cis* and *trans* isomers of *N*-(4-phenylcyclohexyl)imidazole, and without requiring ring inversion, which would place the phenyl axial. We are continuing to use this method to compare the effective size of other substituents, both cationic and anionic, with that of the corresponding neutral.[21]

## Summary and Conclusions

The $A$ value of an *N*-imidazolyl group is 2.2 ± 0.1 kcal/mol, intermediate between that of methyl and phenyl. The $A$ value is solvent independent. The $A$ value of a protonated imidazolyl is 2.2 ± 0.1 kcal/mol. Thus within experimental error, there is no change in the $A$ value of an imidazolyl group upon *N*-protonation. However, by the more accurate titration method the protonated imidazolyl substituent is detectably "larger" than the unprotonated. In aqueous acetone the additional energy required to place the protonated substituent axial is 0.089 ± 0.004 kcal/mol. In $CD_2Cl_2$ this energy is lower, and in DMSO-$d_6$ it reverses.

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(21) Perrin, C. L.; Fabian, M. A., to be published.