Stereodynamics of 1,3,5-Trialkyl-1,3,5-triazacyclohexanes: ^{1}H and ^{13}C Dynamic NMR Studies. Solvent Effects. Ab Initio and Molecular Mechanics Calculations

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Abstract: The ^{1}H NMR signal due to the ring methylene protons of 1,3,5-trimethyl-1,3,5-triazacyclohexane (**TMTAC**), 1,3,5-triethyl-1,3,5-triazacyclohexane (**TETAC**), 1,3,5-tri-isopropyl-1,3,5-triazacyclohexane (**TPTAC**), and 1,3,5-tri-(*tert*-butyl)-1,3,5-triazacyclohexane (**TBTAC**) decoalesces over the temperature range from 330 down to 190 K due to the slowing of chair-to-chair interconversion. Free energies of activation ($\Delta G^{\ddagger} = 12.8-10.3$ kcal/mol) decrease with increasing steric bulk of the alkyl substituents. At temperatures below 200 K, in solvents that do not hydrogen-bond to nitrogen, the ^{1}H and ^{13}C{^{1}H} NMR spectra show a second decoalescence due to slowing inversion at nitrogen. Under conditions of slow chemical exchange, the spectra of all four compounds show a strong preference for three equivalent monoaxial conformations. No other conformations are detected. Free energies of activation for interconversion among monoaxial conformations via sequential inversions at nitrogen ($\Delta G^{\ddagger} = 7.3-5.7$ kcal/mol) decrease with increasing steric bulk of the alkyl substituents. For **TBTAC**, this work constitutes a rare, unequivocally documented case of a preferred axial *tert*-butyl group unconstrained by any counterpoised substituent on the chair conformation of a saturated six-membered ring. The data also establish a strong preference for the monoaxial conformations in **TETAC** and **TPTAC**. In a solvent that can hydrogen-bond to nitrogen (CHF_2Cl), **TMTAC** and **TETAC** show a strong preference for the monoaxial conformations, but they also show about 1% of the triequatorial conformation at 120−130 K, providing evidence for mitigation of the anomeric effect by hydrogen-bonding. **TPTAC** shows only monoaxial conformations in CHF_2Cl; the triequatorial conformation is not detected. In a dramatic reversal of conformational preference, **TBTAC** in CHF_2Cl shows only the triequatorial conformation at 112 K. Barriers to conformational interconversion, via nitrogen inversion, increase in CHF_2Cl, consistent with hydrogen-bonding to nitrogen. Attempts to calculate the energies of 1,3,5-trialkyl-1,3,5-triazacyclohexane equilibrium conformations using available molecular mechanics force fields were unsuccessful. Changes in three torsional constants in the MMX (PCMODEL) force field give significantly improved agreement with experiment and with ab initio (HF/6-31G*) calculations. The modified MMX (PCMODEL) force field was also used to study the effect of hydrogen-bonding by methanol on the conformational energies of the 1,3,5-trialkyl-1,3,5-triazacyclohexanes. These calculations are in remarkably good agreement with the experimental NMR data in CHF_2Cl, including the reversal of conformational preference in **TBTAC**, providing additional support for mitigation of the anomeric effect by hydrogen-bonding.

Introduction

Saturated six-membered rings are prevalent in organic chemistry. For cyclohexane, experimental and computational studies have established that the chair conformation is 5.5 kcal/mol more stable than the twist form.[1−7] In contrast, the chair conformation of cyclohexasilane is only 0.4 kcal/mol more stable than the twist form.[8] The twist conformation of 3,3,6,6-tetramethyl-1,2,4,5-tetrathiacyclohexane is more stable than the chair form by 0.5 kcal/mol.[9]

For monosubstituted cyclohexanes, there is a general, but not exclusive, preference for the equatorial over the axial conformation.[5] Moreover, while chlorocyclohexane prefers the equatorial conformation by 0.5 kcal/mol, *trans*-1,4-dichlorocyclohexane

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prefers the diequatorial conformer by only 0.2 kcal/mol.[5,10] Transannular dipole−dipole attractions are clearly opposing steric repulsions in determining conformational preference in *trans*-1,4-dichlorocyclohexane.

Saturated six-membered heterocycles that contain one or more nitrogen atoms generally show a strong preference for the chair conformation over the twist form.[11] This is analogous to the case with cyclohexane. However, for these saturated multinitrogen six-membered rings that contain multiple bond dipole moments, individual substituent conformational preferences can deviate significantly from those observed in cyclohexane analogues.[11] The 1,3,5-trialkyl-1,3,5-triazacyclohexane system is a case in point. Early dipole moment studies of 1,3,5-trimethyl-1,3,5-triazacyclohexane suggested a preference for two types of equilibrium conformation. One conformation has one axial and two equatorial methyl groups, and the other has one equatorial and two axial methyl groups.[12] The study suggested that little of the triequatorial conformation is present. A subsequent ^{1}H dynamic NMR (DNMR) study of 1,3,5-trimethyl-1,3,5-triazacyclohexane showed an apparently exclusive presence of the three equivalent monoaxial conformers.[13] A later ^{13}C DNMR study confirmed the ^{1}H DNMR results.[14] However, it must be noted that the NMR spectra used in both of these reports were recorded at relatively low observation frequencies with low inherent signal-to-noise ratios. Any signals due to minor conformations might have gone undetected.

In light of the fact that methylcyclohexane prefers the equatorial conformation by 1.7 kcal/mol,[5] the strong preference for the monoaxial conformations in 1,3,5-trimethyl-1,3,5-triazacyclohexane is remarkable. This preference is due to an undetermined partition of factors including reduced steric repulsions between the axial methyl group and the syn-axial nitrogen lone pairs[11] and a preferential orientation of bond dipoles, i.e., the anomeric effect.[2,15] In a monoaxial conformer, the equatorial nitrogen lone pair is vicinal and anti to two electronegative nitrogen atoms. This orientation enhances n−σ* orbital overlap, postulated to be an important stabilization associated with the anomeric effect.[15] Dipole−dipole interactions, and possibly other factors, including diminished n−σ* orbital overlap, destabilize the triequatorial conformation. *syn*-1,3-Dimethyl repulsions destabilize the diaxial conformation.

Previous reports employing ^{13}C DNMR spectra suggest a preference for the monoaxial conformations of 1,3,5-triethyl-1,3,5-triazacyclohexane and 1,3,5-tri-isopropyl-1,3,5-triazacyclohexane.[14] Definitive spectra under conditions of slow chemical exchange were not reported. Based on dipole moment measurements, it has also been suggested that 1,3,5-tri-(*tert*-butyl)-1,3,5-triazacyclohexane prefers the monoaxial conformations.[12,16] It is noteworthy that dipole moment measurements were misleading in the case of 1,3,5-trimethyl-1,3,5-triazacyclohexane.[11a] A preference for an axial *tert*-butyl group has been observed in constrained systems. For example, in *cis*-2-methyl-5-(*tert*-butyl)-1,3-dioxane, the chair conformation with *tert*-butyl axial and methyl equatorial is preferred.[17] However, in this case, the *tert*-butyl group is constrained to be axial by the counterpoised *cis*-2-methyl group that shows a greater preference for the equatorial orientation than the *cis*-(*tert*-butyl) group. It must be noted that 5-(*tert*-butyl)-1,3-dioxane does show a 1.4 kcal/mol preference for the equatorial conformation.[17] This preference is 3.5 kcal/mol lower than that in *tert*-butylcyclohexane and is due, presumably, to the smaller steric size of oxygen lone pairs as compared to protons.

This paper reports ^{1}H and ^{13}C DNMR studies of the 1,3,5-trimethyl-, 1,3,5-triethyl-, 1,3,5-tri-isopropyl- and 1,3,5-tri-(*tert*-butyl)-1,3,5-triazacyclohexanes in a variety of solvents. The tri-isopropyl and tri-(*tert*-butyl) derivatives were especially intriguing in light of the substantial preference of isopropylcyclohexane (2.2 kcal/mol) and *tert*-butylcyclohexane (4.9 kcal/mol) for the equatorial conformer.[5] In solvents that do not hydrogen-bond to nitrogen (CF_2Cl_2, CH_2═$CHCH_3$, CH_2═$CHCl$), the NMR spectra of all four triazacyclohexanes at slow chemical exchange reveal the presence of only the monoaxial conformers. For 1,3,5-tri-(*tert*-butyl)-1,3,5-triazacyclohexane, this paper reports a rare, unequivocally documented example of a preferred axial *tert*-butyl group unconstrained by any counterpoised substituents on the chair conformation of a saturated six-membered ring. While we were pursuing this research, an interesting report did appear showing that 1,3,5-trineopentyl-1,3,5-triazacyclohexane in CF_2Cl_2 at 147 K exists as 9% triequatorial and 91% monoaxial conformations.[18] In our studies in a solvent that does hydrogen-bond to nitrogen (CHF_2Cl),[19] the trimethyl and triethyl derivatives show a strong preference for monoaxial conformations, but they also show about 1% of the triequatorial conformation at 130 K. The tri-isopropyl derivative shows only monoaxial forms. For 1,3,5-tri-(*tert*-butyl)-1,3,5-triazacyclohexane in CHF_2Cl, only the triequatorial conformation is detected. Consistent with previous studies, hydrogen-bonding by CHF_2Cl slows the rate of nitrogen inversion in the triazacyclohexanes compared to the solvents that do not hydrogen-bond.[20]

Molecular mechanics calculations have been useful in providing insight into the stereodynamics of acyclic amines.[21] However, calculation of conformational energies for the 1,3,5-trialkyl-1,3,5-triazacyclohexanes using the MM2(87),[22] MMX (PCMODEL),[23] and MM3(94)[24] force fields were not quantitatively accurate. In this paper, we report modifications of the MMX force field that give substantially better agreement with experimentally determined 1,3,5-trialkyl-1,3,5-triazacyclohexane conformational preferences and with ab initio calculations. The

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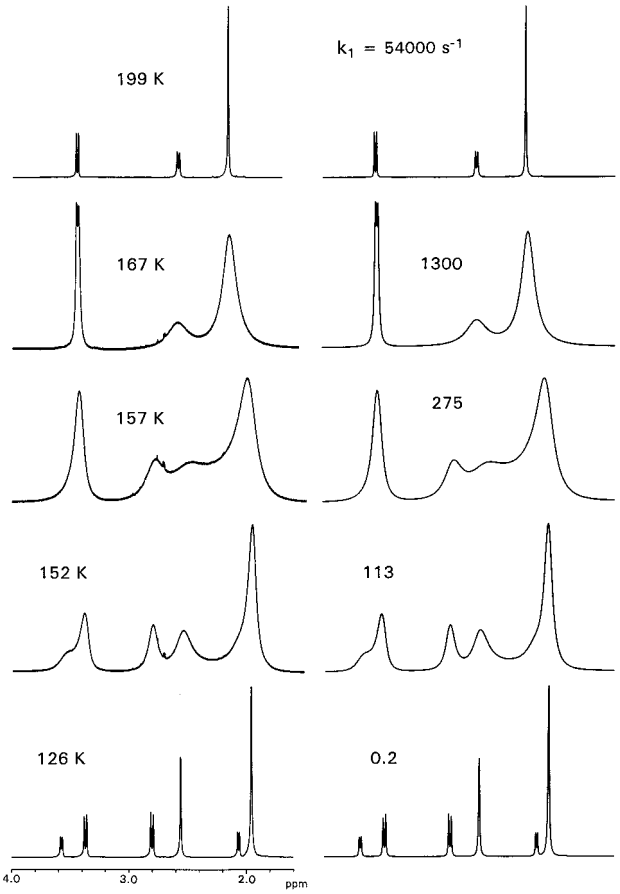


Figure 1. Experimental ^{1}H DNMR spectra (500.16 MHz) of 1,3,5-trimethyl-1,3,5-triazacyclohexane (3% v/v in CF_2Cl_2) in the left column and theoretical simulations in the right column. The rate constant (k_1) is associated with conversion of one monoaxial conformation to one other monoaxial conformer.

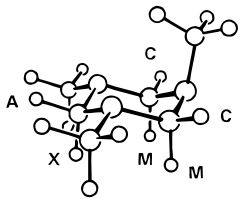
MMX force field is parametrized to treat hydrogen-bonding to alcohols, amines, and thiols. Using the modified MMX amine force field, calculations of the energies of 1,3,5-trialkyl-1,3,5-triazacyclohexane conformations that are hydrogen-bonded to methanol agree with the NMR data in the hydrogen-bonding CHF_2Cl. The calculations correctly predict the switch of conformational preference for the *tert*-butyl derivative from the monoaxial conformations in a non-hydrogen-bonding solvent system to triequatorial in a hydrogen-bonding solvent.

DNMR Studies

1,3,5-Trimethyl-1,3,5-triazacyclohexane. The ^{1}H NMR spectrum (250.14 MHz) of 1,3,5-trimethyl-1,3,5-triazacyclohexane (**TMTAC**; 3% v/v in toluene-d_8) at 340 K shows a singlet resonance at 2.15 ppm (9H) due to the methyl groups and a differentially broadened singlet at 3.06 ppm (6H) due to the methylene protons. At lower temperatures, the resonance due to the methylene protons decoalesces due to slowing chair-to-chair interconversion and, at 210 K, is sharpened into an AX spectrum with chemical shifts at 3.39 ("A") and 2.53 ("X") ppm ($^2J_{AX} = -10.0$ Hz).[25,26] At 210 K, the methyl resonance at 2.10 ppm remains a singlet. Simulations of the DNMR spectra due to the methylene protons gave the rate constants for chair-to-chair interconversion as a function of temperature compiled in Table 1S (Supporting Information).[27] The activation parameters for chair-to-chair interconversion ($\Delta H^{\ddagger} = 13.3 \pm 0.4$ kcal/mol, $\Delta S^{\ddagger} = 1.4 \pm 2.0$ cal mol^{-1} K^{-1}, $\Delta G^{\ddagger} = 12.9 \pm 0.1$ kcal/mol at 280 K) are in good agreement with those previously reported.[25,26] The activation parameters in the gas phase ($\Delta H^{\ddagger} = 13.2 \pm 0.5$ kcal/mol, $\Delta S^{\ddagger} = 1.4 \pm 1.8$ cal mol^{-1} K^{-1}, $\Delta G^{\ddagger} = 12.8 \pm 0.2$ kcal/mol at 288 K)[26] are identical within experimental error to those in toluene-d_8.

The ^{1}H NMR spectrum (500.16 MHz) of **TMTAC** (3% v/v in CF_2Cl_2) at 199 K shows the AX spectrum due to the methylene protons at 3.46 and 2.59 ppm ($^2J_{AX} = -10.1$ Hz), consistent with slow ring reversal on the NMR chemical exchange time scale. The spectrum also shows a singlet resonance for the methyl groups at 2.17 ppm (Figure 1). The methylene protons signal at 2.59 ppm is differentially broadened due to the onset of slowing nitrogen inversion.[13,14]

At temperatures below 199 K, the ^{1}H NMR spectrum of **TMTAC** shows a complex decoalescence due to slowing inversion at nitrogen and is sharpened into a slow-exchange spectrum at 126 K (Figure 1).[13,14] In the 126 K spectrum, the methylene protons show an AX spectrum (2H) with chemical shifts at 3.58 ("A") and 2.07 ("X") ppm ($^2J_{AX} = -7.9$ Hz) and two CM spectra (4H) with chemical shifts at 3.38 ("C") and 2.81 ("M") ppm ($^2J_{CM} = -11.2$ Hz). The methyl groups show singlet resonances at 2.56 (3H) and 1.96 ppm (6H). The spectrum at 126 K shows only the three equivalent monoaxial conformations (**eea**, **eae**, **aee**) of **TMTAC** (e.g., see **1**).[13,14]



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Signals due to other diastereomeric conformers are not observed. The doublets at 3.58 and 2.07 ppm are assigned respectively to the equatorial ("A") and axial ("X") protons in **1**. The axial "X" proton is subject to the well-established shielding of a proton that is vicinal and anti to a nitrogen lone pair; indeed, the "X" proton is anti to two lone pairs.[28] The relatively small coupling between the geminal "A" and "X" protons ($^2J_{AX} = -7.9$ Hz) is typical of an NCH_2N methylene group that has the axial proton vicinal and anti to two nitrogen lone pairs.[29] The two CM spectra (4H) are assigned to the other two methylene groups in **1**, with the chemical shift for the two enantiotopic equatorial protons ("C") at 3.38 ppm and the enantiotopic axial protons ("M") at 2.81 ppm. The axial "M" protons are subject to the reduced shielding of just one anti lone pair. The larger two-bond coupling between geminal "C" and "M" protons ($^2J_{CM} = -11.2$ Hz) is typical of an NCH_2N methylene group that has the axial proton vicinal and anti to one nitrogen lone pair and gauche to a second lone pair.[30] The methyl signal at 2.56 ppm (3H) is assigned to the axial methyl group, and that at 1.96

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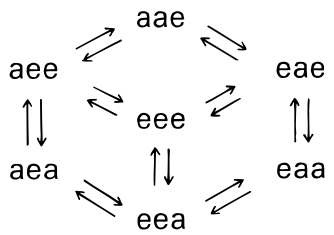
Scheme 1. Conformational Exchange via Nitrogen Inversion among Various Stable and Unstable Equilibrium Conformations of a Chair Conformer of 1,3,5-Trimethyl-1,3,5-triazacyclohexane (**e** = Equatorial Methyl; **a** = Axial Methyl)



ppm (6H) is assigned to the two equatorial methyl groups. The protons on the axial methyl group are subject to steric compression deshielding.[33]

With ring reversal slow on the NMR chemical exchange time scale at 199 K, the DNMR spectra of **TMTAC** below 199 K reflect the slowing of interconversion among the three monoaxial forms of **TMTAC** by sequential inversions at nitrogen.[13] Both ab initio and molecular mechanics calculations (vide infra) clearly indicate that the three equivalent diaxial conformers (**eaa**, **aea**, **aae**) and the triequatorial form (**eee**) are equilibrium conformations, albeit significantly less stable than the monoaxial conformations. Therefore, conformational exchange among the dominant **eea**, **eae**, and **aee** conformers of **TMTAC** involves the **eaa**, **aea**, **aae**, and **eee** forms as unstable intermediates and proceeds via sequential single inversions at nitrogen, e.g., **eea** to **eaa** to **eae**, **eea** to **eee** to **eae**, etc. For a chair conformer of **TMTAC**, all the interconversion pathways are illustrated in Scheme 1. During the interconversion of the **eea**, **eae**, and **aee** conformers, equatorial ring protons remain equatorial and axial protons remain axial. Therefore, the DNMR spectra of the methylene protons in **TMTAC** were simulated by invoking exchange of magnetization among AX, CM, and CM spin systems (see **1**); the DNMR spectra due to the methyl protons were simulated by invoking exchange among three equally populated singlet resonances at 2.56, 1.96, and 1.96 ppm.[27] Superposition of the methylene and methyl protons spectra and iterative adjustment of the rate constant for exchange gave the spectral fits at various temperatures illustrated in Figure 1. The rate constant (k_1) reflects the rate of conversion of one monoaxial form to one other. Because the diaxial and triequatorial conformers are undetected and do not contribute to the DNMR line shape, it is not possible to determine the relative rates of interconversion associated with the two different interconversion pathways (Scheme 1). The free energy of activation ($\Delta G^{\ddagger}$) for an **eea**-to-**eae** conversion is 7.3 ± 0.2 kcal/mol at 152 K. We hesitate to report $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values for the rate processes detected because of the error in temperature measurement (±3 K) on the 500-MHz NMR spectrometer used. The data suggest a small positive entropy of activation ($\Delta S^{\ddagger} \approx 3$ cal mol^{-1} K^{-1}) for the interconversion. The $\Delta G^{\ddagger}$ value in CF_2Cl_2 (7.3 ± 0.2 kcal/mol at 152 K) is within experimental error of that in CH_2=CHCl (7.2 ± 0.1 kcal/mol at 151 K).[13] $\Delta G^{\ddagger}$ values for conformational interconversions in all four 1,3,5-trialkyl-1,3,5-triazacyclohexanes are compiled in Table 1.

The $^{13}C\{^1H\}$ NMR spectrum (125.76 MHz) of **TMTAC** (10% v/v in CF_2Cl_2) at 218 K shows two singlets at 40.52 (methyl carbons) and 77.99 ppm (methylene carbons), as shown in Figure 1S (Supporting Information). At lower temperatures, the signal due to the methyl carbons decoalesces into two singlets at 41.67 (1C; axial methyl) and 40.16 ppm (2C; equatorial methyls). The signal due to the methylene carbons also decoalesces into two singlets at 80.91 (1C; ring carbon flanked by two equatorial methyl groups; see **1**) and 75.70 ppm (2C). No other signals are detected at 126 K. Consistent with the ^1H NMR data, the spectrum at 126 K (Figure 1S) shows only the three monoaxial conformations of **TMTAC**. The DNMR spectra of each of the methyl and methylene carbon resonances were simulated accurately by employing exchange of magnetization among three singlet resonances. The free energy of activation ($\Delta G^{\ddagger}$) for conversion of one monoaxial form to another is 7.2 ± 0.2 kcal/mol at 161 K, in good agreement with the value from the ^1H DNMR data (Table 1).

Table 1. Free Energies of Activation ($\Delta G^{\ddagger}$) for Conformational Interconversions in 1,3,5-Trialkyl-1,3,5-triazacyclohexanes

solvent	process	$\Delta G^{\ddagger}$, kcal/mol (K)
1,3,5-Trimethyl-1,3,5-triazacyclohexane (**TMTAC**)		
CF_2Cl_2	**eea** to **eae**	7.3 ± 0.2 (152 K)
CH_2=CHCl	**eea** to **eae**	7.2 ± 0.1 (151 K)[a]
CHF_2Cl	**eea** to **eae**	7.8 ± 0.2 (167 K)
	eea to **eaa**	7.6 ± 0.2 (167 K)
	eea to **eee**	8.2 ± 0.2 (167 K)
50% CF_2Cl_2/50% CHF_2Cl	**eea** to **eae**	7.8 ± 0.2 (170 K)
	eea to **eaa**	7.5 ± 0.2 (170 K)
	eea to **eee**	8.2 ± 0.2 (170 K)
1,3,5-Triethyl-1,3,5-triazacyclohexane (**TETAC**)		
CF_2Cl_2	**eea** to **eae**	6.4 ± 0.2 (137 K)
50% CF_2Cl_2/50% CHF_2Cl	**eea** to **eae**	6.9 ± 0.2 (147 K)
	eea to **eaa**	6.7 ± 0.2 (147 K)
	eea to **eee**	7.4 ± 0.2 (147 K)
1,3,5-Tri-isopropyl-1,3,5-triazacyclohexane (**TPTAC**)		
CF_2Cl_2	**eea** to **eae**	5.7 ± 0.2 (122 K)
50% CF_2Cl_2/50% CHF_2Cl	**eea** to **eae**	6.7 ± 0.2 (137 K)
1,3,5-Tri-(*tert*-butyl)-1,3,5-triazacyclohexane (**TBTAC**)		
70% CH_2=CHCl/30% CH_2=$CHCH_3$	**eea** to **eae**	5.8 ± 0.2 (118 K)
	eea to **eee**	5.6 ± 0.2 (118 K)
50% CF_2Cl_2/50% CHF_2Cl	unknown	5.7 ± 0.2 (117 K)

[a] See ref 13.

The dipole moments of the **eea**, **eee**, **eaa**, and **aaa** conformations of **TMTAC** calculated by using the MM2(87) molecular mechanics force field are respectively 1.153, 1.911, 0.593, and 1.111 D.[22] Compared to the relatively small dielectric constant of CF_2Cl_2 ($\epsilon = 2.13$), the dielectric constant of CHF_2Cl ($\epsilon = 6.11$) is appreciably larger and should lead to an increased preference for conformers having larger dipole moments, e.g., the **eee** form. In addition, there is evidence from gas-phase studies that CHF_2Cl can hydrogen-bond about as effectively as methanol.[19] Such hydrogen-bonding will alter dipole−dipole interactions in the various triazane conformations and could, in principle, alter n−σ* orbital overlap. Both effects could mitigate the anomeric effect.

The ^1H NMR spectrum (500.16 MHz) of **TMTAC** (3% v/v in CHF_2Cl) at 218 K (Figure 2S, Supporting Information) shows the AX spectrum due to the methylene protons at 3.61 and 2.71 ppm ($^2J_{AX} = -10.1$ Hz), consistent with slow ring reversal on the NMR chemical exchange time scale. The spectrum also shows a singlet resonance for the methyl groups at 2.24 ppm. The $^{13}CH_3$ isotopomer doublet is observed at 2.24 ppm ($^1J_{CH} = 135$ Hz). This has been incorporated into the simulation at 218 K. A singlet resonance due to an impurity at 2.18 ppm broadens and disappears from the spectra below 170 K. Other impurity resonances are observed between 2.75 and 2.85 ppm; these remain sharp down to 127 K.

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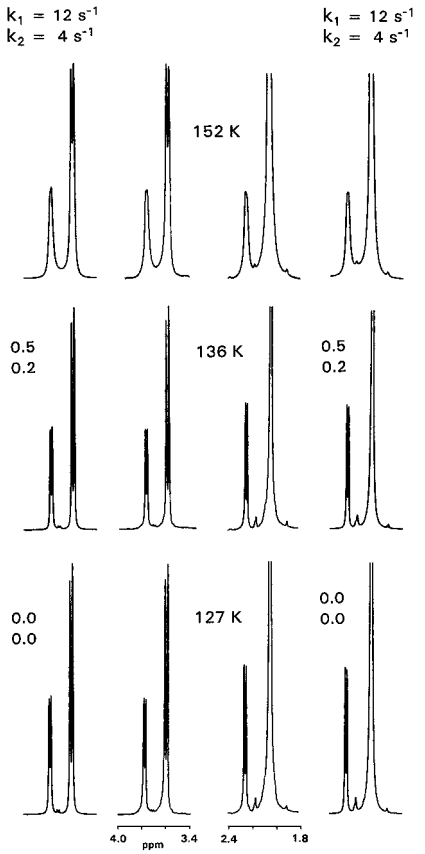


Figure 2. Amplifications of selected regions of the experimental ^{1}H DNMR spectra (500.16 MHz) of 1,3,5-trimethyl-1,3,5-triazacyclohexane (3% v/v in CHF_2Cl) in the middle columns and theoretical simulations in the outside columns. Signals due to the $^{13}CH_3$ isotopomers are included in the simulations. The rate constant (k_1) is associated with conversion of one monoaxial conformation to one other monoaxial conformer. The rate constant (k_2) is associated with conversion of one monoaxial conformation to the triequatorial form.

At temperatures below 218 K, the spectrum of **TMTAC** in CHF_2Cl decoalesces in a manner analogous to that of **TMTAC** in CF_2Cl_2 (Figure 1), but with some notable differences. The 167 K spectrum in Figure 2S is more decoalesced than the 167 K spectrum in Figure 1, revealing a slower rate of nitrogen inversion in CHF_2Cl than in CF_2Cl_2. At slow exchange in CHF_2Cl (127 K spectrum in Figure 2S), the spectrum is dominated by signals due to the monoaxial conformations. The methylene protons show an AX spectrum (2H) with chemical shifts at 3.78 ("A") and 2.27 ("X") ppm ($^2J_{AX} = -8.2$ Hz) and two CM spectra (4H) with chemical shifts at 3.60 ("C") and 3.02 ("M") ppm ($^2J_{CM} = -11.0$ Hz). The methyl groups show singlet resonances at 2.64 (3H) and 2.06 ppm (6H). It is noteworthy that all the methylene protons' chemical shifts in CHF_2Cl are at higher frequency ("lower field") by 0.2 ppm than those in CF_2Cl_2. This is consistent with hydrogen-bonding by CHF_2Cl.[19,20] The spectrum at 127 K shows a clear dominance of the monoaxial conformations. However, the spectrum at 127 K also shows minor signals that are too intense to be associated with any impurity signals observed at 218 K. In particular, there is a doublet signal observed at 3.71 ppm. Amplifications of selected regions of the spectrum are shown in Figure 2. The separation between the lines in the doublet at 3.71 ppm is 8.0 Hz; this is the magnitude of a typical geminal coupling constant for an NCH_2N ring methylene group that has the axial proton vicinal and anti to *two* nitrogen lone pairs.[29] Other than the unique methylene moiety in the monoaxial form (see protons "A" and "X" on structure **1**), the only other chair conformation that would give such a signal and show this coupling is the **eee** form. Indeed, all three axial protons on the **eee** conformation are homotopic and anti to two nitrogen lone pairs. This signal is logically assigned to the three homotopic equatorial protons on the **eee** form. Of course, assigning this signal to the equatorial protons on the **eee** conformation requires the presence of a sister doublet due to the axial protons at a chemical shift that should be near the "X" resonance of the monoaxial conformations (see **1** and Figure 1), i.e., a large shift to lower frequency ("higher field") as compared to the signal for the equatorial protons. A careful inspection of the equatorial methyl signal at 2.06 ppm at 127 K (Figure 2) shows more inflections on the higher frequency base of the peak than on the lower frequency side, suggesting the presence of minor signals. Indeed, as shown in Figure 3S (Supporting Information), narrow-band homonuclear irradiation near 2.06 ppm results in the collapse of the minor doublet at 3.71 ppm to a singlet, confirming the presence of a BZ spin system with widely divergent chemical shifts at 3.71 ("B") and about 2.11 ("Z") ppm ($^2J_{BZ} = -8.0$ Hz). This is rigorously consistent with the molecular geometry of the **eee** conformer. Additionally, a minor singlet resonance is observed at 2.18 ppm in the 127 K spectrum (Figure 2) that overlaps the higher frequency component of the equatorial $^{13}CH_3$ isotopomer doublet. This singlet has a chemical shift close to that of the equatorial methyl groups of the monoaxial conformations (2.06 ppm) and is logically assigned to the equatorial methyl groups on the **eee** conformer. Consistent with the structure of the **eee** conformer, simulations of the spectrum at 127 K employed an area ratio of the minor singlet at 2.18 ppm to the BZ spectrum equal to 3:2. As shown in Figure 2, these minor signals broaden and coalesce into the dominant spectrum at higher temperatures, consistent with their being associated with the triazane molecular system. Complete line shape simulation at 127 K (Figures 2 and 2S), including incorporation of the $^{13}CH_3$ doublet due to the equatorial methyl groups, shows that the spectral area for the **eee** conformer is about 1.0% of that due to the three monoaxial conformations.[27] This corresponds to an equilibrium constant between the triequatorial conformer and one monoaxial form ([**eea**]/[**eee**]) equal to 33:1 or a free energy preference for the **eea** conformer over the **eee** of 0.9 ± 0.1 kcal/mol at 127 K.

Simulations of the DNMR spectra in Figures 2 and 2S invoked an exchange of magnetization among dominant AX, CM, and CM spin systems (monoaxial conformers) and the minor BZ spin system (triequatorial form) for the methylene protons. For the methyl groups, simulations invoked exchange among four singlet resonances, including three equally populated singlets for the dominant monoaxial forms and one minor singlet for the **eee** form. This exchange matrix is constrained by the fact that rates of exchange among the AX, CM, and CM spin systems and among the three methyl singlets of the monoaxial forms must be equal. Additionally, it was necessary to increase the population of the **eee** conformer as the temperature increased in order to obtain line-on-line fits of the spectra. In Figures 2 and 2S, k_1 is the rate constant for conversion of one monoaxial form to one other monoaxial conformer; k_2 is the rate constant for conversion of one monoaxial form to the triequatorial. The $\Delta G^{\ddagger}$ value for conversion of one monoaxial conformer to one other monoaxial form is 7.8 ± 0.2 kcal/mol at 167 K. The $\Delta G^{\ddagger}$ value for conversion of one monoaxial conformer to the triequatorial form is 8.2 ± 0.2 kcal/mol at 167 K. Presuming that an **eaa** conformer is an unstable equilibrium conformation and therefore an intermediate in the interconversion of **eea** and **eae** conformers (Scheme 1), the rate constant for the **eea**-to-

eaa conversion is twice k_1. Thus, the $\Delta G^{\ddagger}$ value for the **eea**-to-**eaa** nitrogen inversion process is 7.6 ± 0.2 kcal/mol at 167 K, or 0.6 kcal/mol lower than that for the **eea**-to-**eee** nitrogen inversion (Table 1).

The presence of a detectable population of the **eee** conformer in CHF_2Cl, and not in CF_2Cl_2, is due at least in part to the higher dielectric constant of CHF_2Cl. A 50% CHF_2Cl/50% CF_2Cl_2 solvent system should have a bulk dielectric constant intermediate between those of the two pure solvents. If the dielectric constant were the only factor to be considered, the population of the **eee** form in the 50% CHF_2Cl/50% CF_2Cl_2 solvent system should be lower than that in pure CHF_2Cl.

At temperatures below 215 K, the spectrum of **TMTAC** in 50% CF_2Cl_2/50% CHF_2Cl (Figure 4S, Supporting Information) decoalesces in a manner that is virtually identical to that for **TMTAC** in pure CHF_2Cl (Figure 2S). At 132 K (Figure 4S), the spectrum is dominated by signals due to the monoaxial conformations. The **eee** conformation shows a BZ spectrum at 3.71 and 2.11 ppm ($^2J_{BZ} = -8.4$ Hz) due to the methylene protons and a methyl singlet at 2.18 ppm. Amplifications of selected regions of the DNMR spectra are shown in Figure 5S (Supporting Information). Complete line shape simulation[27] at 132 K shows the spectral area due to the **eee** conformer to be about 1.4% of that due to the three monoaxial conformations, corresponding to a free energy preference for the **eea** conformer over the **eee** of 0.8 ± 0.1 kcal/mol at 132 K. Within experimental error, this free energy difference is identical to that in pure CHF_2Cl (0.9 ± 0.1 kcal/mol at 127 K).

The ^{1}H DNMR spectra of **TMTAC** in 50% CF_2Cl_2/50% CHF_2Cl were simulated by using an exchange matrix that is identical to that used for the simulations in pure CHF_2Cl. The various free energies of activation are listed in Table 1. Within experimental error, the free energies of activation in 50% CF_2Cl_2/50% CHF_2Cl are identical to those in CHF_2Cl (Table 1).

The population of the **eee** conformer is the same within experimental error in 50% CF_2Cl_2/50% CHF_2Cl and in pure CHF_2Cl. This suggests that bulk dielectric is not a dominant factor in determining conformational preference. It would appear that the stabilization of the **eee** conformer relative to the **eea** form in 50% CF_2Cl_2/50% CHF_2Cl and in CHF_2Cl is due in large part to a mitigation of the anomeric effect by hydrogen-bonding. In 50% CF_2Cl_2/50% CHF_2Cl, it appears that CHF_2Cl preferentially solvates **TMTAC**, resulting in virtually identical populations of the **eee** conformer in 50% CF_2Cl_2/50% CHF_2Cl and in pure CHF_2Cl.

The ^{13}C{^{1}H} NMR spectrum (125.76 MHz) of **TMTAC** (10% v/v in 50% CF_2Cl_2/50% CHF_2Cl) shows signals due to the methyl carbons at 40.44 ppm and due to the methylene carbons at 78.20 ppm (Figure 3). At lower temperatures, the spectrum decoalesces and is sharpened into a slow-exchange spectrum at 126 K. At 126 K, the methyl carbons show dominant signals for the monoaxial conformers at 41.23 ppm due to the axial methyl group and at 39.65 ppm due to the equatorial methyl groups. A minor singlet is observed at 40.22 ppm near the signal due to the equatorial methyl groups of the monoaxial forms, with an integrated area that is 1% of the area due to both methyl signals of the monoaxial conformers. The intensity of this resonance is equal to the **eee** population determined from the ^{1}H NMR data. This peak is logically assigned to the **eee** conformation. At 126 K, the methylene carbons show two signals at 80.91 (1C) and 75.62 (2C) ppm. No minor peak for the **eee** conformer is detected in this region of the spectrum, suggesting signal overlap. The exchange-broadened 165 K

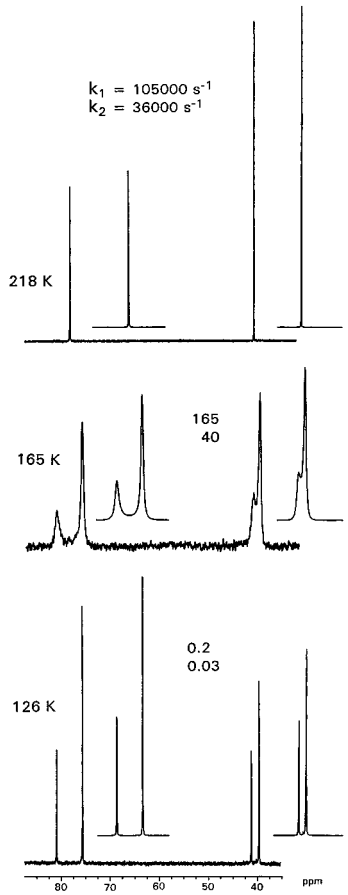


Figure 3. Experimental ^{13}C{^{1}H} DNMR spectra (125.76 MHz) of 1,3,5-trimethyl-1,3,5-triazacyclohexane (10% v/v in 50% CF_2Cl_2/50% CHF_2Cl) and theoretical simulations above and to the right. The rate constants are defined in the caption to Figure 2.

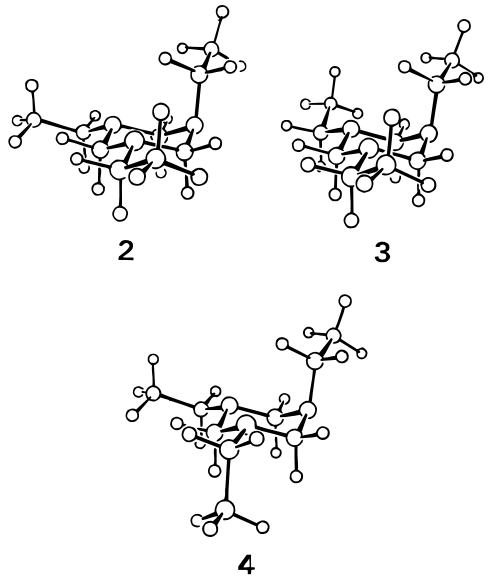
spectrum in Figure 3 was simulated by invoking an exchange of magnetization among three dominant methyl carbon singlets at 41.23, 39.65, and 39.65 ppm and the minor peak at 40.22 ppm. This exchange matrix is identical to that used to simulate the ^{1}H DNMR spectra of the methyl groups (Figure 4S). A strictly analogous exchange matrix was used to simulate the ^{13}C{^{1}H} DNMR spectra of the methylene carbons with dominant chemical shifts at 80.91, 75.62, and 75.62 ppm and the minor peak presumed to be at 80.91 ppm. The fit at 165 K (Figure 3) is very good and gives rate constants for interconversions that agree with the ^{1}H DNMR results.

1,3,5-Triethyl-1,3,5-triazacyclohexane. The ^{1}H NMR spectrum (250.14 MHz) of 1,3,5-triethyl-1,3,5-triazacyclohexane (**TETAC**; 3% v/v in toluene-d_8) at 300 K shows the quartet (2.39 ppm) and triplet (0.99 ppm; $^3J_{HH} = 7.1$ Hz) due to the ethyl groups and a broad singlet at 3.26 ppm ($W_{1/2} = 10$ Hz) due to the ring methylene protons. At lower temperatures, the signal due to the ring methylene protons decoalesces and, at 220 K, is sharpened into an AX spectrum with chemical shifts at 3.73 ("A") and 2.68 ("X") ppm ($^2J_{AX} = -10.0$ Hz). The resonances due to the ethyl groups are unchanged at 220 K. Simulations of the DNMR spectra[27] due to the ring methylene protons (Table 1S) gave activation parameters for chair-to-chair interconversion ($\Delta H^{\ddagger} = 13.4 \pm 0.4$ kcal/mol, $\Delta S^{\ddagger} = 3.8 \pm 2.0$ cal mol^{-1} K^{-1}, $\Delta G^{\ddagger} = 12.4 \pm 0.1$ kcal/mol at 260 K) that agree with those previously reported.[14,25b]

The ^{1}H NMR spectrum (500.16 MHz) of **TETAC** (3% v/v in CF_2Cl_2) at 199 K shows the quartet (2.39 ppm) and triplet (1.04 ppm; $^3J_{HH} = 7.2$ Hz) due to the ethyl groups. The

methylene protons show an AX spectrum at 3.72 and 2.64 ppm ($^2J_{AX} = -10.0$ Hz). The spectrum of **TETAC** between 4.2 and 1.6 ppm shows a complex decoalescence at temperatures below 199 K due to slowing inversion at nitrogen (Figure 4) and is sharpened into a slow-exchange spectrum at 117 K. The spectrum at 117 K is rigorously consistent with a strong preference for the monoaxial conformations.

At 117 K, rotation about the exocyclic N−C bonds that interconverts conformations such as **2**, **3**, and **4** is fast on the DNMR time scale.[31] With rapid isolated rotation about all



exocyclic N−C bonds, the time-averaged symmetry of a monoaxial conformer of **TETAC** is C_s. The chemical shifts of the methylene protons on the axial ethyl group will be time-averaged to one value. However, the methylene protons on each equatorial ethyl group are diastereotopic. Their molecular environments cannot be mutually interchanged by internal rotation or any symmetry operation. In principle, they will show two different chemical shifts in a time-averaged C_s-symmetric monoaxial conformer.

Complete line shape simulation at 117 K shows a widely spaced AY spectrum (2H) with chemical shifts at 3.85 ("A") and 1.96 ("Y") ppm ($^2J_{AY} = -8.0$ Hz), and two CN spectra (4H) at 3.64 ("C") and 2.78 ("N") ppm ($^2J_{CN} = -11.0$ Hz) for the ring methylene protons. In a manner strictly analogous to that of **TMTAC** (vide supra), the spectrum due to the ring methylene protons of **TETAC** is rigorously consistent with the molecular geometry of the monoaxial conformation. The AY spectrum is assigned to the methylene group between the two equatorial ethyl groups; the CN spectra are assigned to the two methylene groups that flank the axial ethyl group.

Consistent with time-averaged C_s symmetry, the ethyl methylene protons show three signals at 2.84, 2.16, and 2.03 ppm at 117 K (Figure 4). These signals are simulated accurately by invoking one M_2Z_3 spectrum (5H; axial ethyl) with chemical shifts at 2.84 ("M") and 1.10 ("Z") ppm ($^3J_{MZ} = 7.0$ Hz), and two VXZ_3 spectra (10H; equatorial ethyl groups) at 2.16 ("V"), 2.03 ("X"), and 1.10 ppm ("Z") with $^3J_{VZ} = 7.5$ Hz, $^3J_{XZ} = 6.5$ Hz, and $^2J_{VX} = -12.0$ Hz. Superposition of the spectra due to the ring methylene and ethyl groups gave an excellent fit of the 117 K spectrum. There was no need to invoke any other resonances to achieve an accurate spectral simulation, indicating a strong preference for the monoaxial conformations. No other conformations are detected.

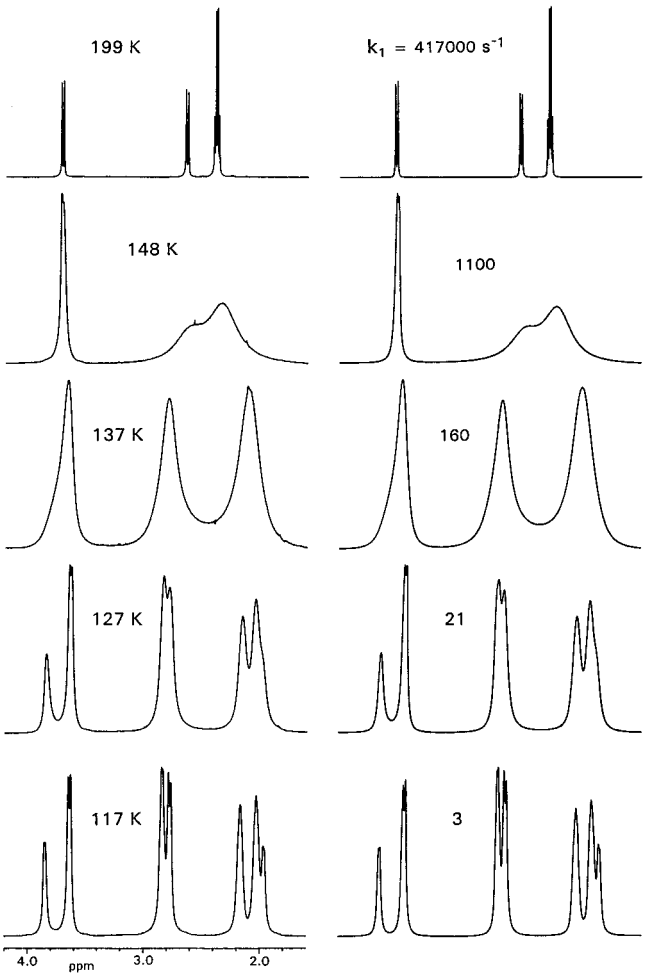


Figure 4. Experimental ^{1}H DNMR spectra (500.16 MHz) of the methylene groups in 1,3,5-triethyl-1,3,5-triazacyclohexane (3% v/v in CF_2Cl_2) in the left column and theoretical simulations in the right column. The rate constant (k_1) is associated with conversion of one monoaxial conformation to one other monoaxial conformer.

As shown in Figure 6S (Supporting Information), the methyl signal shows broadening at lower temperatures, but no decoalescence into separate, resolved resonances, revealing an insensitivity to being axial or equatorial. The chemical shift of the methyl groups at 117 K (1.10 ppm) is typical of methyl groups that are oriented vicinal and gauche to the lone pair, and not anti, showing an apparent preference for conformations such as **2** or **3**, and not **4**.[28a]

The ^{1}H DNMR spectra of **TETAC** were simulated by invoking equal rates of magnetization exchange among AY, CN, and CN spin systems for the ring methylene protons and among M_2Z_3, VXZ_3, and XVZ_3 spectra for the ethyl groups. The rate constant (k_1) in Figure 4 reflects the rate of conversion of one monoaxial form to one other. The free energy of activation ($\Delta G^{\ddagger}$) for an **eea**-to-**eae** conversion is 6.4 ± 0.2 kcal/mol at 137 K (Table 1).

The ^{13}C{^{1}H} NMR spectrum (125.76 MHz) of **TETAC** (10% v/v in CF_2Cl_2) at 198 K shows three singlets at 13.14 (methyl carbons), 47.17 (methylene carbons on ethyl groups), and 74.68 ppm (ring methylene carbons), as shown in Figure 7S (Supporting Information). At lower temperatures, all three resonances decoalesce into two signals, and, at 117 K, the spectrum shows methyl carbon resonances at 13.65 (1C) and 12.05 (2C) ppm, ethyl methylene carbon signals at 46.89 (2C) and 46.57 (1C) ppm, and ring carbon peaks at 77.32 (1C) and 72.85 (2C) ppm. No other resonances are detected. The spectrum at 117 K

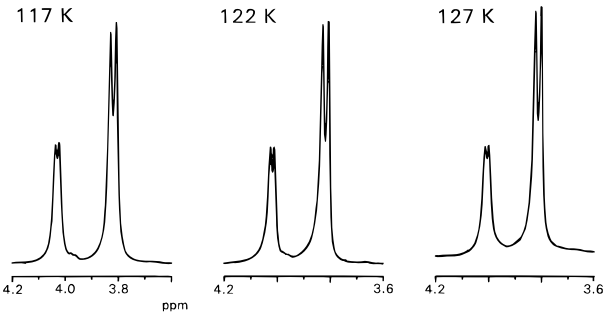


Figure 5. Amplification of a selected region of the experimental ^{1}H DNMR spectra (500.16 MHz) of 1,3,5-triethyl-1,3,5-triazacyclohexane (3% v/v in 50% CF_2Cl_2/50% CHF_2Cl).

confirms the strong preference of **TETAC** for the monoaxial conformations. The free energy of activation ($\Delta G^{\ddagger}$) for conversion of one monoaxial form to another is 6.5 ± 0.2 kcal/mol at 139 K, in good agreement with the value from the ^{1}H DNMR data (Table 1).

At temperatures below 199 K, the ^{1}H DNMR spectrum of **TETAC** in 50% CF_2Cl_2/50% CHF_2Cl (Figure 8S, Supporting Information) decoalesces in a manner analogous to that of **TETAC** in CF_2Cl_2 (Figure 4), but with some expected differences. At slow exchange in 50% CF_2Cl_2/50% CHF_2Cl (117 K spectrum in Figure 8S), the spectrum is dominated by signals due to the monoaxial conformations. At 117 K, signals due to the ethyl groups of the monoaxial conformers are simulated by invoking one N_2Z_3 spectrum (5H; axial ethyl) at 2.89 ("N") and 1.10 ("Z") ppm ($^3J_{NZ}$ = 7.0 Hz) and two RVZ_3 spectra (10H; equatorial ethyl groups) at 2.29 ("R"), 2.16 ("V"), and 1.10 ppm ("Z") with $^3J_{RZ} = {}^3J_{VZ}$ = 7.0 Hz and $^2J_{RV}$ = −13.0 Hz. Resonances due to the ring methylene protons of the monoaxial forms are simulated by employing an AU spectrum (2H) at 4.03 ("A") and 2.21 ("U") ppm ($^2J_{AU}$ = −8.0 Hz) and two CM spectra (4H) at 3.83 ("C") and 3.00 ("M") ppm ($^2J_{CM}$ = −11.0 Hz). The chemical shifts due to the methylene protons in 50% CF_2Cl_2/50% CHF_2Cl are at higher frequency ("lower field") by 0.2 ppm than those in CF_2Cl_2, consistent with hydrogen-bonding by CHF_2Cl.[19]

In the 117 K spectrum of **TETAC** in 50% CF_2Cl_2/50% CHF_2Cl (Figure 5), the equatorial ring methylene proton doublet for the **eee** conformation is observed at 3.97 ppm ($^2J_{HH}$ = −8 Hz). As expected, this signal shows coalescence with the dominant monoaxial resonances as the temperature increases. The population of the **eee** conformer is about 1.4% at 117 K, showing a 0.7 kcal/mol free energy preference for one monoaxial conformer over the **eee** at 117 K. This conformational preference is similar to that for **TMTAC** in 50% CF_2Cl_2/50% CHF_2Cl and is consistent with similar steric requirements for methyl and ethyl groups, as reflected by their respective *A* values (1.6 and 1.8 kcal/mol).[5]

As shown in Figure 9S (Supporting Information), the methyl signal shows broadening but no decoalescence into separate, resolved resonances at lower temperatures.

Simulations of the DNMR spectra of the ring methylene protons (Figure 8S) invoked an exchange of magnetization among dominant AU, CM, and CM spin systems (monoaxial conformers) and a BT spin system (3.97 and 2.21 ppm; $^2J_{BT}$ = −8.0 Hz) for the **eee** conformer. The ethyl spectra were simulated by employing magnetization exchange among dominant N_2Z_3, RVZ_3, and VRZ_3 spectra for the monoaxial conformers and a minor S_2Z_3 (2.27 and 1.10 ppm; $^3J_{SZ}$ = 7.0 Hz) spectrum for the triequatorial conformer. Activation parameters are compiled in Table 1.

The $^{13}C\{^1H\}$ NMR spectrum (125.76 MHz) of **TETAC** (10% v/v in 50% CF_2Cl_2/50% CHF_2Cl) at 198 K shows three singlets at 13.10 (methyl carbons), 47.36 (methylene carbons on ethyl groups), and 75.00 ppm (ring carbons), as shown in Figure 10S (Supporting Information). At lower temperatures, two resonances decoalesce. At 117 K, the spectrum shows methyl carbon resonances at 14.16 (1C) and 12.34 (2C) ppm, ring carbon peaks at 77.31 (1C) and 73.00 (2C) ppm, and one singlet due to the ethyl methylene carbons at 43.80 ppm. The chemical shifts of the axial and equatorial ethyl methylene carbons are coincident. Signals due to the **eee** conformer are not detected due to signal overlap and/or inadequate signal-to-noise ratios. The 117 K spectrum does confirm the dominance of the monoaxial conformations. The DNMR spectra of each of the three types of carbon atoms were simulated accurately by employing a chemical exchange matrix identical to that for the ^{1}H DNMR spectra of **TETAC** in 50% CF_2Cl_2/50% CHF_2Cl with chemical shifts for the methyl, ethyl methylene, and ring carbons of the **eee** conformation presumed to be respectively at 12.4, 43.80, and 77.5 ppm. Using this model, a calculated spectrum at 147 K incorporating 2% of the **eee** conformation gave rate constants essentially identical to those determined from the ^{1}H DNMR spectrum at 147 K.

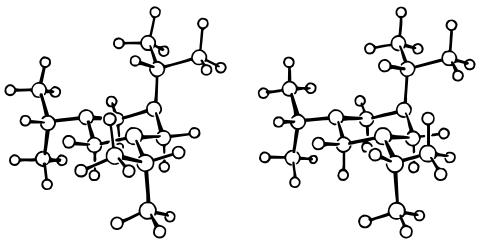
1,3,5-Tri-isopropyl-1,3,5-triazacyclohexane. The ^{1}H NMR spectrum (250.14 MHz) of 1,3,5-tri-isopropyl-1,3,5-triazacyclohexane (**TPTAC**; 3% v/v in toluene-d_8) at 300 K shows a broadened singlet ($W_{1/2}$ = 3.4 Hz) due to the methylene protons at 3.48 ppm. At lower temperatures, this signal decoalesces and, at 190 K, is sharpened into an AX spectrum with chemical shifts at 3.89 ("A") and 3.02 ("X") ppm ($^2J_{AX}$ = −10.0 Hz). Simulations of the DNMR spectra[27] due to the methylene protons (Table 1S) gave activation parameters for chair-to-chair interconversion ($\Delta H^{\ddagger}$ = 11.2 ± 0.4 kcal/mol, $\Delta S^{\ddagger}$ = 0.3 ± 2.0 cal mol^{-1} K^{-1}, $\Delta G^{\ddagger}$ = 11.2 ± 0.1 kcal/mol at 240 K) that agree with those previously reported.[14,25b]

The ^{1}H NMR spectrum (500.16 MHz) of **TPTAC** (3% v/v in CF_2Cl_2) at 199 K shows the septet (2.81 ppm; $^3J_{HH}$ = 6.5 Hz) and doublet (1.03 ppm) due to the isopropyl groups. The methylene protons show an AX spectrum at 3.88 and 2.95 ppm ($^2J_{AX}$ = −10.0 Hz). The spectrum from 4.2 to 2.3 ppm (Figure 11S, Supporting Information) decoalesces at lower temperatures. Below 115 K, the sample froze; the melting point of pure CF_2Cl_2 is 118 K. At 115 K, the methyl groups show a single broad resonance. The decoalescence is best assigned to slowing inversion at nitrogen that interconverts dominant monoaxial conformations of **TPTAC**. Another rate process that could affect the DNMR line shape is isolated rotation about the exocyclic N−C bonds. However, the DNMR-detectable barrier to isolated rotation about the methine carbon−nitrogen bond in isopropyldimethylamine is 4.5 kcal/mol.[32] For **TPTAC**, this speaks for fast rotation about exocyclic N−C bonds on the ^{1}H DNMR time scale at 115 K.

The 115 K spectrum is subject to broadening due to a moderate rate of chemical exchange. The 115 K spectrum can be simulated accurately by employing equal rates of exchange of magnetization (k_1 = 40 s^{-1}) among three equally populated septet resonances at 2.60, 2.60, and 3.32 ppm ($^3J_{HH}$ = 6.5 Hz) due to the methine protons and among equally populated AX, AX, and CY spin systems due to the methylene protons with chemical shifts at 3.84 ("A"), 3.04 ("X"), 3.65 ("C"), and 2.94 ("Y") ppm. $^2J_{AX}$ and $^2J_{CY}$ values were presumed to be −11 and −8 Hz, respectively. The chemical shifts for the ring methylene protons in the monoaxial conformations of **TPTAC** are different from those in **TMTAC** and **TETAC** (vide supra).

These chemical shift changes are consistent, at least in part, with the effects of steric compression due to the additional methyl groups in **TPTAC**.[33] The area ratio of the methine proton signal at 3.32 ppm to that at 2.60 ppm is exactly 1:2. The chemical shift difference (0.72 ppm) between these two resonances is characteristic of protons on axial and equatorial carbon atoms on the trialkyltriazane chair conformation (vide supra). The spectrum at 115 K is consistent with a strong preference for the monoaxial conformations of **TPTAC**. The free energy of activation ($\Delta G^{\ddagger}$) for conversion of one monoaxial conformation to one other monoaxial conformer is 5.7 ± 0.2 kcal/mol at 122 K (Table 1).

The $^{13}C\{^1H\}$ NMR spectrum (125.76 MHz) of **TPTAC** (10% v/v in CF_2Cl_2) at 199 K shows three singlets at 20.19 (methyl carbons), 50.23 (methine carbons), and 68.95 ppm (methylene carbons), as shown in Figure 12S (Supporting Information). At lower temperatures, all three resonances decoalesce. At 115 K, the ^{13}C NMR spectrum is substantially more sharply defined than the ^1H NMR spectrum at 115 K, reflecting greater ^{13}C chemical shift dispersion and different chemical exchange time scales for the ^1H and ^{13}C spectra. At 115 K (Figure 12S), the methyl carbons show three equally populated and differentially broadened signals at 18.30, 18.99, and 21.71 ppm. The methine carbons signal is decoalesced into two singlets at 51.81 (2C) and 46.49 (1C) ppm. The methylene carbons also show just two resonances at 69.95 (1C) and 66.77 (2C) ppm. No other resonances are detected. The spectrum at 115 K is consistent with a strong preference of **TPTAC** for the monoaxial conformations. With slow interconversion among monoaxial conformations and rapid isolated rotation about all exocyclic N−C bonds,[32] the time-averaged symmetry of a monoaxial conformer is C_s. The stereochemical relationship between methyl groups on each isopropyl group is strictly analogous to that between methylene protons on each ethyl group of a monoaxial conformation of **TETAC** (vide supra). The methyl carbons on the axial isopropyl group in **TPTAC** will show one singlet, while the diastereotopic methyl carbons on each of the equatorial isopropyl groups will, in principle, show two different signals. This is consistent with the observation of three methyl carbon signals at 115 K. In simulating the 115 K spectrum, it was necessary to invoke significantly longer effective transverse relaxation times for the methine carbon signals as compared to the methylene and certain methyl carbon signals. This is consistent with the onset of slowing isolated rotation about equatorial exocyclic N−C bonds (e.g., interconversion among conformations **5** and **6** and others) that differentially broadens methylene and methyl carbon signals.[32] The free energy of



5 **6**

activation ($\Delta G^{\ddagger}$) for conversion of one monoaxial form to another (5.7 ± 0.2 kcal/mol at 131 K) is in good agreement with the value from the ^1H DNMR data (Table 1).

In a solvent that does not hydrogen-bond to nitrogen (CF_2Cl_2), there is a strong preference for the monoaxial conformations of **TPTAC**. No other conformations are detected. This is remarkable in light of the strong preference for the equatorial conformation of isopropylcyclohexane (2.2 kcal/mol)[5] and attests to a significant stabilization of the monoaxial conformations of **TPTAC** due to the anomeric effect.

As shown in Figure 13S (Supporting Information), the ^1H DNMR spectrum (500.16 MHz) of **TPTAC** (3% v/v in 50% CF_2Cl_2/50% CHF_2Cl) decoalesces at lower temperatures, reaching slow exchange at 119 K. The 119 K spectrum is simulated accurately by invoking methine proton septets at 3.17 (1H; $^3J_{HH}$ = 6.0 Hz) and 2.69 ppm (2H; $^3J_{HH}$ = 6.0 Hz) in addition to a CY spectrum (2H) at 3.77 and 3.13 ppm ($^2J_{CY} = -7.7$ Hz) and two AX spectra (4H) at 3.98 and 3.19 ppm ($^2J_{AX} = -11.0$ Hz) for the methylene protons. The 119 K spectrum is consistent with a strong preference for the monoaxial conformations of **TPTAC**. We could not locate any other signals in the 119 K spectrum that might be due to minor conformations. The free energy of activation ($\Delta G^{\ddagger}$) for conversion of one monoaxial form to another is 6.7 ± 0.2 kcal/mol at 137 K.

The $^{13}C\{^1H\}$ NMR spectrum (125.76 MHz) of **TPTAC** (10% v/v in 50% CF_2Cl_2/50% CHF_2Cl) decoalesces below 199 K, reaching slow exchange at 126 K (Figure 6). At 126 K, the spectrum shows methylene carbon signals at 72.09 (1C) and 66.86 (2C) ppm, methine carbon resonances at 52.45 (2C) and 48.02 (1C) ppm, and methyl carbon signals at 21.89 (2C), 19.80 (2C), and 18.15 (2C) ppm. No other signals due to the **eee** conformation were detected. The spectrum at 126 K is rigorously consistent with the time-averaged C_s molecular symmetry of the monoaxial conformation of **TPTAC** (vide supra) and a strong preference for the monoaxial conformations. At 126 K and below (Figure 6), differential transverse relaxation times were used to simulate differential broadening due to the onset of slowing equatorial isopropyl group rotation.[32] The free energy of activation ($\Delta G^{\ddagger}$) for conversion of one monoaxial form to another is 6.7 ± 0.2 kcal/mol at 141 K, in excellent agreement with the barrier obtained from the ^1H DNMR data (Table 1).

1,3,5-Tri-(*tert*-butyl)-1,3,5-triazacyclohexane. The ^1H NMR spectrum (250.14 MHz) of 1,3,5-tri-(*tert*-butyl)-1,3,5-triazacyclohexane (**TBTAC**; 3% v/v in toluene-d_8) at 296 K shows a singlet due to the *tert*-butyl protons (27H) at 1.12 ppm and a singlet due to the methylene protons (6H) at 3.74 ppm that decoalesces at lower temperatures due to slowing chair-to-chair interconversion. At 190 K, the methylene protons show an AX spectrum with chemical shifts at 4.30 ("A") and 3.18 ("X") ppm ($^2J_{AX} = -10.4$ Hz). Simulations of the DNMR spectra[27] due to the methylene protons (Table 1S) gave activation parameters for ring inversion ($\Delta H^{\ddagger} = 10.2 \pm 0.4$ kcal/mol, $\Delta S^{\ddagger} = -0.3 \pm 2.0$ cal mol^{-1} K^{-1}, $\Delta G^{\ddagger} = 10.3 \pm 0.1$ kcal/mol at 225 K) that agree with those previously reported.[14,25b]

The ^1H NMR spectrum (500.16 MHz) of **TBTAC** in a solvent system that cannot hydrogen-bond to nitrogen (3% v/v in 70% $CH_2{=}CHCl$/30% $CH_2{=}CHCH_3$) at 177 K shows the *tert*-butyl singlet at 1.11 ppm and an AX spectrum at 4.24 and 3.06 ppm ($^2J_{AX} = -10.0$ Hz) due to the methylene protons. It is interesting to note that, especially for this *tert*-butyl derivative, the $^2J_{AX}$ value is a typical time-averaged value for a trialkyltriazane that shows a strong preference for monoaxial conformations (vide supra). There is a singlet observed at 1.14 ppm due to a persistent impurity that has an intensity about twice that for either component of the $^{13}CH_3$ isotopomer doublet at 1.11 ppm ($^1J_{CH} = 125$ Hz). This impurity signal remains a singlet down to 105 K. At temperatures below 140 K, the signals due to the methylene protons (Figure 7) and the *tert*-butyl protons (Figure 8) decoalesce. Both decoalescence phenomena are consistent with a major presence of the monoaxial conformations of

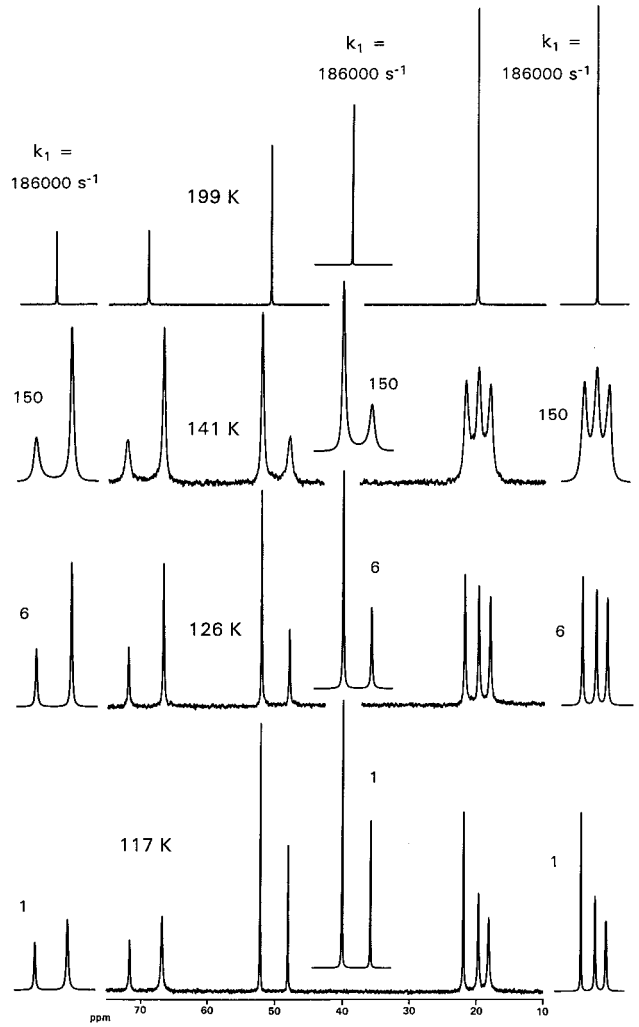


Figure 6. Experimental $^{13}C\{^1H\}$ DNMR spectra (125.76 MHz) of 1,3,5-tri-isopropyl-1,3,5-triazacyclohexane (10% v/v in 50% CF_2Cl_2/50% CHF_2Cl) and theoretical simulations of spectra due to the methylene carbons to the left, due to the methine carbons above and to the right, and due to the methyl carbons to the right. The rate constant (k_1) is associated with conversion of one monoaxial conformation to one other monoaxial conformer. At temperatures below 126 K, differential transverse relaxation times were used to simulate differential broadening due to the onset of isolated rotation about equatorial exocyclic N−C bonds.

TBTAC. Not only do both signals decoalesce in response to slowing interconversion among the monoaxial conformations, but the *tert*-butyl resonance also shows decoalescence into multiple signals, consistent with both nitrogen inversion and *tert*-butyl rotation being slow at 105 K. Decoalescence of the spectra due to both the *tert*-butyl and methylene protons is inconsistent with a strong preference for the C_{3v}-symmetric **eee** conformation, which would show no decoalescence for the methylene protons below 190 K but could show decoalescence of the *tert*-butyl signal. In this instance, C_{3v} symmetry also requires that the *tert*-butyl groups will show just two signals with a 2:1 intensity ratio. The 105 K spectrum (Figure 8) shows four singlets.

At 105 K (Figure 7), the methylene protons show a sharpened, slow-exchange spectrum that is simulated by invoking two AM spectra (4H) at 4.29 ("A") and 3.15 ("M") ppm ($^2J_{AM} = -11$ Hz) and one BN spectrum (2H) at 4.13 ("B") and 2.87 ("N") ppm ($^2J_{BN} = -8$ Hz). No other signals are observed. Broad lines due to rapid transverse relaxation and signal overlap could hide minor signals. Due to the broad lines, the larger $^2J_{AM}$ coupling is barely resolved. The smaller $^2J_{BN}$ coupling is an estimate determined by an iterative fit of the spectrum at 105 K. Using the same transverse relaxation times ($T_2^* = 0.022$ s; $W_{1/2} = 14.5$ Hz) for all methylene protons at 105 K, a $^2J_{BN}$ value of −9 Hz produces B and N signals with flat tops that do not reflect the experimental spectrum; a $^2J_{BN}$ value of −6 Hz produces B and N signals that are clearly sharper than the experimental spectrum.

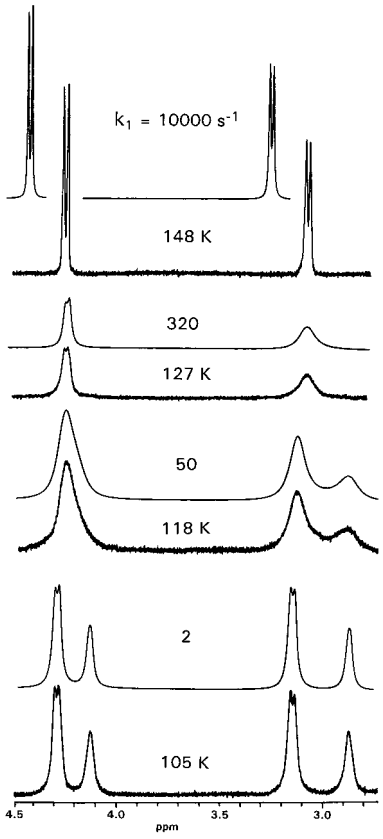


Figure 7. Experimental ^1H DNMR spectra (500.16 MHz) of the methylene protons of 1,3,5-tri-(*tert*-butyl)-1,3,5-triazacyclohexane (3% v/v in 70% $CH_2{=}CHCl$/30% $CH_2{=}CHCH_3$) and theoretical spectra. The rate constant (k_1) is associated with conversion of one monoaxial conformation to one other monoaxial conformer.

The spectrum of the methylene protons of **TBTAC** at 105 K is strictly analogous to that due to the methylene protons on the monoaxial conformation of **TPTAC**, is consistent with the molecular symmetry of the monoaxial conformation of **TBTAC**, and reveals a strong preference for the three equivalent monoaxial conformations. The BN spectrum (2H) with the smaller $^2J_{BN}$ value is assigned to the unique methylene group flanked by two equatorial *tert*-butyl groups; the two AM spectra (4H) with the larger $^2J_{AM}$ value are assigned to the other two methylene groups that flank the axial *tert*-butyl group. As compared to the spectra of **TPTAC**, the chemical shifts due to the equatorial protons on the monoaxial conformation of **TBTAC** are shifted significantly (0.45−0.48 ppm) to higher frequency, consistent with enhanced steric compression deshielding due to the additional methyl group on *tert*-butyl.[33]

The DNMR spectra of **TBTAC** in Figure 7 are simulated accurately by employing equal rates of exchange among equally populated AM, AM, and BN spin systems with no compelling need to invoke additional spectra due to minor conformations. The free energy of activation ($\Delta G^{\ddagger}$) for conversion of one monoaxial form to another is 5.8 ± 0.2 kcal/mol at 118 K.

As shown in Figure 8, the signal due to the *tert*-butyl protons decoalesces and, at 105 K, shows four resolved albeit broad

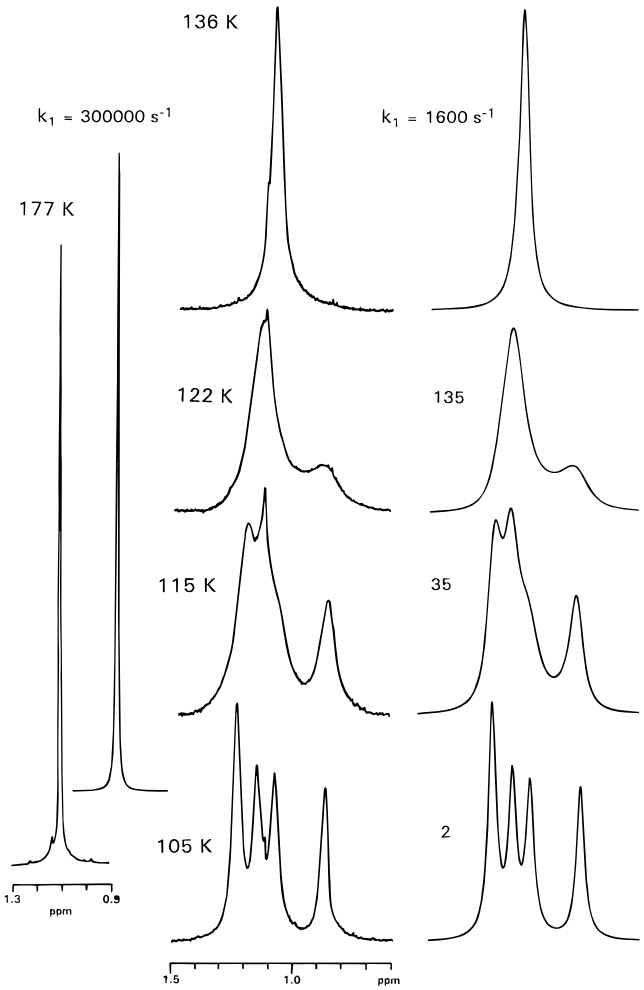


Figure 8. Experimental ^{1}H DNMR spectra (500.16 MHz) of the *tert*-butyl groups of 1,3,5-tri-(*tert*-butyl)-1,3,5-triazacyclohexane (3% v/v in 70% CH_2═$CHCl$/30% CH_2═$CHCH_3$) and theoretical spectra displayed to the right. The rate constant (k_1) is associated with conversion of one monoaxial conformation to one other monoaxial conformer.

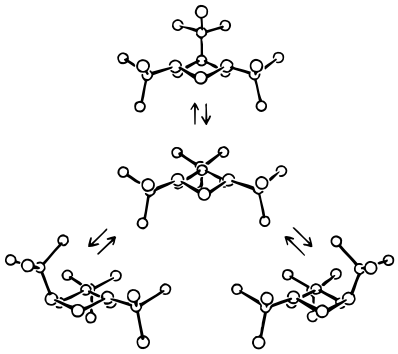
($W_{1/2}$ = 19 Hz; T_2* = 0.017 s) singlets at 1.23 (9H), 1.15 (6H), 1.08 (6H), and 0.87 ppm (6H). The impurity signal is still a relatively sharp singlet at 105 K and appears on the low-frequency side of the *tert*-butyl signal at 1.15 ppm. The fact that the methyl groups on the *tert*-butyl moieties show singlet resonances at 105 K indicates that isolated rotation of individual methyl groups in **TBTAC** is fast on the DNMR chemical exchange time scale at 105 K.[32] The spectrum of the methylene protons of **TBTAC** at 105 K shows a clear preference for the monoaxial conformations. With nitrogen inversion and *tert*-butyl rotation slow at 105 K, the spectrum due to the *tert*-butyl groups in a C_s-symmetric monoaxial conformer should, in principle, show five singlets; it shows four. The 105 K spectrum can be interpreted in essentially two different ways. In one interpretation, axial *tert*-butyl rotation is very fast and equatorial *tert*-butyl rotation is slow at 105 K. Under these conditions, the singlet at 1.23 ppm (9H) would have to be assigned to the axial *tert*-butyl group, and the singlets at 1.15 (6H), 1.08 (6H), and 0.87 (6H) ppm would be assigned to the three diastereotopic methyl groups on each of the two equatorial *tert*-butyl moieties. An alternative interpretation would require that the chemical shifts of all methyl groups on the axial *tert*-butyl moiety are coincident; in this case, axial *tert*-butyl rotation could be fast or slow at 105 K. In either case, all signals due to the axial *tert*-butyl group occur at the same chemical shift. In the other interpretation, axial and equatorial *tert*-butyl rotations are both slow at 105 K. For the axial *tert*-butyl group, the signal due to the unique methyl group that is anti to the lone pair and oriented over the ring overlaps a 6H singlet due to two other enantiotopic methyl groups at 1.23 ppm; the signal due to the other two enantiotopic methyl groups on the axial *tert*-butyl group occurs at some other frequency.

The slow-exchange spectrum at 105 K can be simulated accurately by employing chemical shifts assignments based on either interpretation presented above. Either interpretation is consistent with the C_s molecular symmetry of the monoaxial conformation. However, attempts to simulate the *tert*-butyl DNMR spectra over a wide temperature range were not successful when using chemical shift assignments based on the first interpretation. Acceptable internally consistent fits of the DNMR spectra over a wide temperature range were obtained by employing axial *tert*-butyl chemical shifts at 1.08 (6H; two methyl groups) and 1.23 ppm (3H; one methyl group) and equatorial *tert*-butyl signals at 1.23 (6H), 1.15 (6H), and 0.87 (6H) ppm. The chemical shift at 0.87 ppm due to two methyl groups is typical of methyl groups that are oriented vicinal and anti to the nitrogen lone pair in *tert*-butyldialkylamines.[21,31,34] For the monoaxial conformation of **TBTAC**, this signal is assigned to the methyl group that is anti to the lone pair on each of the two equatorial *tert*-butyl moieties. For the axial *tert*-butyl moiety, the methyl group that is anti to the lone pair, and over the ring, is apparently subject to steric compression deshielding. Acceptable fits of the exchange-broadened *tert*-butyl DNMR spectra (Figure 8) were then obtained by employing a chemical exchange matrix that allows no direct exchange of magnetization among three axial *tert*-butyl frequencies at 1.08 (3H), 1.08 (3H), and 1.23 (3H) ppm and no direct exchange among equatorial *tert*-butyl signals at 1.23 (6H), 1.15 (6H), and 0.87 (6H) ppm. The chemical exchange matrix does allow complete exchange between the two sets of axial and equatorial *tert*-butyl signals; i.e., each of the three axial *tert*-butyl frequencies exchanges with all three equatorial frequencies. This matrix allows indirect exchange of equatorial frequencies via axial frequencies, and vice versa. In simulating the DNMR spectra in Figure 8, good fits were obtained by employing a rate of transfer of magnetization from each of the axial signals to each of the equatorial resonances that is equal to the rate of interconversion between monoaxial conformations determined from simulations of the methylene protons' DNMR spectra (Figure 7). This is analogous to the stereodynamics of *tert*-butyldialkylamines in which the lowest barrier process for interconverting *tert*-butyl methyl groups among different molecular environments is *tert*-butyl rotation that occurs in concert with nitrogen inversion.[21,34] The lowest barrier process that interconverts methyl groups among various molecular environments in **TBTAC** is *tert*-butyl rotation that occurs in concert with inversion at nitrogen, i.e., interconversion among monoaxial conformations. The implication is that isolated rotation barriers for axial and equatorial *tert*-butyl groups in **TBTAC** are equal to or higher than that for nitrogen inversion. Barriers to isolated axial *tert*-butyl rotation (6.4 kcal/mol) and equatorial *tert*-butyl rotation (7.5 kcal/mol) calculated using a reparametrized MMX (PCMODEL) molecular mechanics force field support this interpretation (vide infra).

Molecular mechanics calculations (vide infra) predict that the **eaa** conformation of **TBTAC** is 14.5 kcal/mol less stable than the **eea** form. The barrier to nitrogen inversion in **TBTAC** is

(34) Bushweller, C. H.; Anderson, W. G.; Stevenson, P. E.; Burkey, D. L.; O'Neil, J. W. *J. Am. Chem. Soc.* **1974**, *96*, 3892.

Scheme 2. Conformational Exchange via Nitrogen Inversion among Various Stable and Unstable Equilibrium Conformations of One Chair Conformer of 1,3,5-tri-(*tert*-butyl)-1,3,5-triazacyclohexane (Protons Have Been Deleted for Clarity)



5.8 kcal/mol. In contrast to **TMTAC**, for which equilibrium **eaa** and **eee** conformations are accessible unstable intermediates in the interconversion of the monoaxial conformations (Scheme 1), the **eaa** conformer of **TBTAC** is not a reasonable intermediate in the interconversion of the monoaxial forms of **TBTAC**. The only reasonable unstable intermediate is the **eee** conformation. Thus, it would appear that any two monoaxial conformations of **TBTAC** interconvert via the **eee** conformation as the sole intermediate (Scheme 2). Presuming that the **eee** conformer is an unstable equilibrium conformation and the intermediate in the interconversion of monoaxial conformers (Scheme 2), the rate constant for an **eea** to **eee** conversion is twice k_1 in Figure 7. The $\Delta G^{\ddagger}$ value for an **eea**-to-**eee** nitrogen inversion process is 5.6 ± 0.2 kcal/mol at 118 K.

Based on dipole moment measurements, it has been suggested that **TBTAC** prefers the **eea** over the **eee** conformation by 0.35 kcal/mol at 298 K.[12] Dipole moment measurements were misleading in the case of **TMTAC**.[11a] We believe that the DNMR data presented above provide unequivocal evidence for clearly preferred monoaxial conformations in **TBTAC**. This is a rare, unequivocally documented case of a preferred axial *tert*-butyl group that is unconstrained by any counterpoised substituent on the chair conformation of a six-membered ring. In contrast to the 4.9 kcal/mol preference for equatorial *tert*-butylcyclohexane,[5] the significant switch in conformational preference in **TBTAC** is due, in part, to the small steric size of axial lone pairs on nitrogen.[11] The nearly isosteric 5-(*tert*-butyl)-1,3-dioxane shows a 1.4 kcal/mol preference for the equatorial conformation,[17] 3.5 kcal/mol lower than that in *tert*-butylcyclohexane, attesting to the smaller steric size of lone pairs as compared to protons. The anomeric effect does not influence the conformational preference of the *tert*-butyl group in 5-(*tert*-butyl)-1,3-dioxane. However, the monoaxial conformation of **TBTAC** does derive additional stabilization from the anomeric effect, leading to its preference over the **eee** form.

The ^{1}H NMR spectrum (500.16 MHz) due to the methylene protons of **TBTAC** in a hydrogen-bonding solvent (3% v/v in 50% CF_2Cl_2/50% CHF_2Cl) at 180 K shows an AX spectrum with chemical shifts at 4.27 and 2.81 ppm ($^2J_{AX} = -7.7$ Hz). The small $^2J_{AX}$ value suggests that all three methylene groups have an axial proton anti to two lone pairs, consistent with a strong preference for the **eee** conformation. The chemical shift difference between the A and X resonances is 1.46 ppm, similar to the chemical shift difference between the protons on the unique methylene group of the monoaxial conformation of **TBTAC** (1.26 ppm; Figure 7). At lower temperatures (Figure 14S, Supporting Information), the resonances due to the methylene protons remain essentially unchanged, except for increased line broadening due to increasing rates of transverse relaxation at lower temperatures. No differential broadening or decoalescence is observed. This spectral behavior is rigorously consistent with a strong preference for the C_{3v}-symmetric **eee** conformation of **TBTAC**; all three equatorial protons are homotopic, and all three axial protons are homotopic. With chair-to-chair interconversion slow at 190 K, the methylene protons will show no additional decoalescence below 190 K.

The ^{1}H NMR spectrum of **TBTAC** in 50% CF_2Cl_2/50% CHF_2Cl at 199 K also shows a singlet at 1.11 ppm due to the *tert*-butyl groups, the $^{13}CH_3$ isotopomer doublet (1.11 ppm; $^1J_{CH} = 125$ Hz), and the impurity singlet at 1.18 ppm (Figure 15S, Supporting Information). At lower temperatures, the *tert*-butyl resonance decoalesces, and, at 112 K, it shows two resolved albeit broad singlet resonances at 1.19 (18H) and 0.97 (9H) ppm. The *tert*-butyl signals at 112 K can be simulated accurately by invoking three singlets of equal intensity at 1.19, 1.19, and 0.97 ppm and a rate constant for random exchange among all three singlets equal to 20 s^{-1}. The observation of just two *tert*-butyl chemical shifts is consistent with the C_{3v} symmetry of the **eee** conformer. The signal at 1.19 ppm is assigned to the two enantiotopic methyl groups on each *tert*-butyl group that are vicinal and gauche to the nitrogen lone pair; the signal at 0.97 ppm is assigned to the methyl group on each *tert*-butyl group that is anti to the lone pair.[28a,34] The spectrum of the *tert*-butyl and methylene protons at 112 K is rigorously consistent with the C_{3v} symmetry of the **eee** conformation of **TBTAC**.

While mitigation of the anomeric effect in **TMTAC** and **TETAC** due to hydrogen-bonding by CHF_2Cl results in the presence of about 1% of the **eee** conformation (vide supra), **TBTAC** shows a much stronger preference for the **eee** form. The switch in **TBTAC** conformational preference on going from non-hydrogen-bonding to hydrogen-bonding solvents is remarkable. This enhanced preference for the **eee** conformation in **TBTAC** is due to an additional destabilization of the monoaxial conformers due to increased steric repulsions experienced by the methyl group in the axial *tert*-butyl group that must reside over the ring.

The DNMR spectra in Figure 15S were simulated accurately using the chemical exchange matrix described above for the spectrum at 112 K. The free energy of activation for exchange of magnetization between any two singlets is 5.7 ± 0.2 kcal/mol at 117 K. The DNMR spectra do not allow identification of the rate process associated with the decoalescence in Figure 15S. All that is clear is that chair-to-chair interconversion, nitrogen inversion, and *tert*-butyl rotation are all slow at 112 K.

Ab Initio and Molecular Mechanics Calculations

For **TMTAC**, the MM3(92) molecular mechanics force field[24] predicts the **eee** conformation to be more stable than that of **eea** by 0.17 kcal/mol, with the relative energies of the **eaa** and **aaa** conformations at 3.67 and 8.46 kcal/mol. The MM3(92) relative energies of the **eee** and **eea** conformations are clearly at variance with experiment (vide supra). The MM2(87) force field predicts relative energies for **eea** (0.00 kcal/mol), **eee** (0.13 kcal/mol), **eaa** (4.13 kcal/mol), and **aaa** (11.55 kcal/mol) conformations that are in better qualitative agreement with experiment.[22] However, assuming no difference in entropy between **eee** and **eea** conformations and taking into account the statistical preference for the three monoaxial conformations ($\Delta S = R \ln 3$), the 0.13 kcal/mol preference for **eea** over **eee** would give an easily detectable 17% **eee** at 126 K, which is not

observed. The MMX (PCMODEL, v6.0) force field also predicts a 0.17 kcal/mol preference for the **eea** conformation over **eee**.[23] The MM2(87) and MMX force fields, which both use the Profeta−Allinger amine parameters,[22] predict the correct order of stability for **eea** and **eee** conformations but overestimate the stability of the **eee** form. The MM3, MM2(87) and MMX force fields all incorrectly predict the **eee** conformation of **TBTAC** to be more stable than the **eea** conformation by 0.39, 0.38, and 0.73 kcal/mol, respectively. These discrepancies between the DNMR data and conformational energies calculated by molecular mechanics are not surprising in light of the fact that all three force fields have not been parametrized for the nitrogen anomeric effect. Others have noted similar discrepancies for 1,3,5-trineopentyl-1,3,5-triazacyclohexane.[18]

In principle, extensive parameter changes in the MM2 and MMX force fields [torsional constants, C−N bond moments, lone pair (Lp) "hardness", and effective size] could be required to accurately model the anomeric effect in trialkyltriazacyclohexanes. Based on parameter changes that better model the oxygen anomeric effect,[35a] one obvious adjustment is to increase the N−C−N−Lp V_2 torsional parameter to reflect the stabilization associated with orienting the lone pair vicinal and anti to another nitrogen atom. An increase in this parameter from 0.00 to 1.00 has been used to model the N−C−N effect in bicyclic aminals.[36] This change gives qualitatively acceptable results for **TMTAC**, but quantitative agreement is still wanting. A recent attempt to model the N−C−N effect that employed an extensive adjustment of many parameters does not give reasonable relative energies for the various conformations of **TMTAC**.[37]

We found that the minimal MMX force field changes required to accurately reflect the conformational energetics of all four trialkyltriazacyclohexanes involves three torsions about the N−C−N linkage, consistent with recent attempts to model the oxygen anomeric effect using the MM3 force field.[35b] Specifically, when V_2 torsional parameters for N−C−N−Lp(TOR 166), H−C−N−Lp(TOR 163), and C−C−N−Lp(TOR 154) linkages are changed from 0.00 to 1.00, −1.00, and −0.60, respectively, the MMX force field gives relative conformational energies that are consistent with the experimental observation that, for all four trialkyltriazacyclohexanes (including **TBTAC**), the **eea** conformer is the dominant species detected in non-hydrogen-bonding solvents (Table 2). It should be noted that the N−C−N−Lp and H−C−N−Lp modifications successfully model **TMTAC** and **TBTAC**. The additional C−C−N−Lp change is required to model **TETAC** and **TPTAC** and, therefore, all four trialkyltriazacyclohexanes. Moreover, the latter change gives better agreement between calculated and experimental conformational energies for various acyclic amines.[32,38]

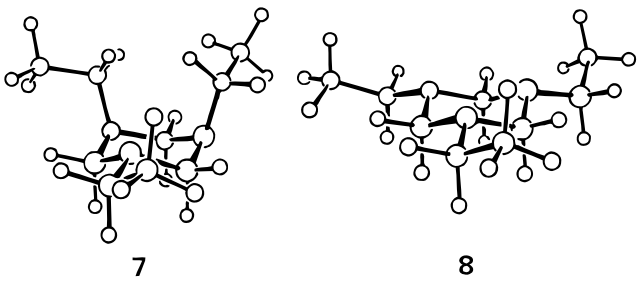
The modified MMX force field ("MMXTAC") calculations predict that the **eaa** and **eee** conformations of **TMTAC** are respectively 1.45 and 2.90 kcal/mol less stable than the **eea** conformation (Table 2). These energy differences are consistent with the DNMR spectrum for **TMTAC** in CF_2Cl_2 at 126 K that shows only monoaxial conformations. An energy difference of about 0.9 kcal/mol will result in a minor conformation being present at a barely NMR-detectable 1% concentration at 125 K (vide supra).

Table 2. Dipole Moments and Relative MMX Energies for Trialkytriazane Conformations Calculated Using Modified Torsional Parameters

compound	conformation	relative energy (kcal/mol)	dipole moment (D)
TMTAC[a]	**eea**	0.00	1.18
	eaa	1.45	0.64
	eee	2.90	1.93
	twist	8.90	0.86
TETAC[b,c]	**eea**	0.00	1.19
	eaa	1.72	0.65
	eee	3.29	1.93
	twist	8.81	0.87
TPTAC[c,d]	**eea**	0.00	1.21
	eee	3.10	1.91
	eaa	4.02	0.69
	twist	8.39	0.87
TBTAC[e]	**eea**	0.00	1.13
	eee	2.11	1.91
	twist	5.38	0.86
	eaa	14.52	0.70

[a] 1,3,5-Trimethyl-1,3,5-triazacyclohexane. [b] 1,3,5-Triethyl-1,3,5-triazacyclohexane. [c] Relative energy of conformation with most stable combination of alkyl group rotamers about exocyclic N−C bonds (see structures **3**, **7**, **8**; **6**, **9**, **10**). [d] 1,3,5-Tri-isopropyl-1,3,5-triazacyclohexane. [e] 1,3,5-Tri-(*tert*-butyl)-1,3,5-triazacyclohexane.

Methyl and *tert*-butyl groups are symmetric rotors. Conformational analysis of **TMTAC** and **TBTAC** is not complicated by the existence of diastereomeric equilibrium conformations resulting from rotation about the exocyclic N−C bonds. However, for **TETAC** and **TPTAC**, three staggered rotamers associated with each of the three exocyclic N−C bonds results in multiple equilibrium conformations for each of the **eea**, **eee**, and **eaa** conformations. In Table 2, the MMXTAC relative energies listed are between the most stable **eea**, **eaa**, and **eee** conformations, i.e, those conformations with the most stable combination of alkyl group rotamers. For **TETAC**, the most stable **eea** conformations are **3**, point group C_1, and its enantiomer. In **3**, a methylene proton on the axial ethyl group is over the ring; placing the methyl group over the ring increases the energy by 1.94 kcal/mol. The methyl groups on the equatorial ethyl moieties in **3** are each gauche to a lone pair, and both point toward the axial ethyl substituent. The various conformations that have all methyl groups gauche to a lone pair all have energies within 0.1 kcal/mol of each other. For an equatorial ethyl group, placing methyl anti to the lone pair (e.g., see **4**) increases the energy by about 0.4 kcal/mol. The most stable **eaa** and **eee** conformations of **TETAC** are **7** (C_1) and **8** (C_3).



7 **8**

For **TPTAC**, the most stable **eea** conformation is the C_s-symmetric **6**. In **6**, the methine proton on the axial isopropyl group is over the ring; placing a methyl group over the ring increases the energy by 1.45 kcal/mol. The methine protons on

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(36) Alder, R. W.; Heilbronner, E.; Honneger, E.; McEwen, A. B.; Moss, R. E.; Olefirowicz, E.; Petillo, P. A.; Sessions, R. B.; Weisman, G. R.; White, J. M.; Yang, Z.-Z. *J. Am. Chem. Soc.* **1993**, *115*, 6580.

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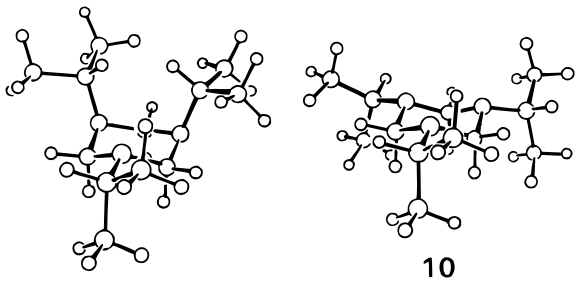
(38) Brown, J. H.; Bushweller, C. H. *J. Am. Chem. Soc.* **1995**, *117*, 12567.

the equatorial isopropyl groups in **6** are each gauche to a lone pair, and both point away from the axial isopropyl substituent. For the equatorial isopropyl groups, conformations that have the methine proton gauche to a lone pair are all within 0.2 kcal/mol of each other; placing the methine proton anti to the lone pair increases the energy by about 0.9 kcal/mol. For each equatorial isopropyl group, this preference for orienting one methyl group gauche and the other anti to the lone pair is consistent with observations in other systems.[32] The most stable **eaa** and **eee** conformations of **TPTAC** are **9** (C_1) and **10** (C_3). In **9**, the methine protons on the axial isopropyl groups are anti to the lone pair and over the ring.



9 **10**

The MMXTAC calculations also predict that the twist conformation of the trialkyltriazacyclohexane ring is about 5−9 kcal/mol less stable than the **eea** chair conformation (Table 2). In Table 2, the relative energies of the most stable twist forms are listed. For **TBTAC**, the twist is predicted to be considerably more stable than the highly distorted **eaa** form. These calculations suggest strongly that all equilibrium conformations of all four trialkyltriazacyclohexanes detected by NMR adopt the chair conformation.

For the **eea** conformations of **TMTAC**, **TETAC**, **TPTAC**, and **TBTAC**, the C−N−(axial carbon) bond angles are respectively 112.1°, 113.5°, 113.7°, and 116.5°, with C−N−(equatorial carbon) bond angles respectively 112.1°, 113.3°, 114.9°, and 115.1°. The progressive increase in these bond angles in proceeding from methyl to *tert*-butyl shows a progressive decrease in pyramidality at nitrogen that is consistent with progressively decreasing nitrogen inversion (Table 1) and chair-to-chair interconversion barriers (vide supra).

Ab initio geometry optimizations of the **eea**, **eaa**, and **eee** conformations of **TMTAC** were computed at the HF/6-31G* level using GAUSSIAN 98W.[39] The relative energies (Table 3) are in good agreement with the MMXTAC molecular mechanics calculations (Table 2). The ab initio dipole moments for the **eea** (1.27 D), **eaa** (0.89 D), and **eee** (2.08 D) conformations of **TMTAC** are also in good agreement with the MMXTAC calculations. There is excellent agreement with various structural parameters; e.g., the ab initio and MMXTAC C−N−(axial C) bond angles in the **eea** conformation are respectively 111.9° and 112.1°. Frequency calculations, performed at the HF/6-31G* level, confirmed that these three chair conformations of **TMTAC** are equilibrium geometries (no imaginary normal modes). These calculations also demonstrated that, while quantitatively significant, zero-point energy corrections do not change the relative order of stability of the **eea**, **eaa**, and **eee** conformations (0.00, 1.70, and 3.50 kcal/mol, respectively). Furthermore, geometry optimizations at the MP2/6-31G* level (Table 3) showed that electron correlation does not change the relative order of stabilities.

Table 3. Ab Initio Energies for Optimized Geometries of Chair Conformations of 1,3,5-Trimethyl-1,3,5-triazacyclohexane

	HF/6-31G*		MP2/6-31G*	
conf.	*E* (hartrees)	rel. energy (kcal/mol)	EUMP2 (hartrees)	rel. energy (kcal/mol)
eea	−399.243382	0.00	−400.518026	0.00
eaa	−399.240985	1.70	−400.516927	1.08
eee	−399.237171	3.50	−400.510826	4.91

Both ab initio and MMXTAC calculations predict a strong preference for the **eea** conformation of **TMTAC** (Tables 2 and 3). Both calculations also predict the **eaa** conformer to be more stable than the **eee** conformer. All of this is consistent with invoking **eaa**, **aea**, **aae**, and **eee** conformations as unstable intermediates in the interconversion of the NMR-detectable monoaxial conformations (Scheme 1).

In a solvent that does not hydrogen-bond (CF_2Cl_2), the NMR spectrum of **TMTAC** at 126 K (Figures 1 and 1S) shows only monoaxial conformations. In a solvent that does hydrogen-bond (CHF_2Cl), the NMR spectrum of **TMTAC** at 127 K (Figures 2 and 2S) shows dominant monoaxial conformations, but it also shows 1% of the **eee** form. No diaxial conformations are detected in either solvent. The ^{1}H NMR spectrum of **TBTAC** in a non-hydrogen-bonding solvent (70% CH_2═$CHCl$/30% CH_2═$CHCH_3$) at 105 K (Figures 7 and 8) shows only monoaxial conformations. In a significant reversal of conformational preference, the ^{1}H NMR spectrum of **TBTAC** in a hydrogen-bonding solvent (50% CF_2Cl_2/50% CHF_2Cl) at 112 K (Figures 14S and 15S) shows a strong preference for the **eee** conformation. It is clear that mitigation of the anomeric effect, due in large part to hydrogen-bonding by CHF_2Cl, reverses the relative energies of **eea** and **eee** conformations. For **TMTAC**, based on the MMXTAC calculations, the mitigation is at least 2.0 kcal/mol.

Ion cyclotron resonance studies have established that CHF_2Cl forms hydrogen bonds to bases that are about as strong as those formed by methanol.[19] The MMX force field is parametrized to prevent hydrogen-bonding by C−H bonds, but it is well-parametrized for hydrogen-bonding involving O−H, N−H, and S−H bonds. In principle, the MMX force field can model the effect of certain hydrogen-bonding solvents on the relative stabilities of various Brönsted bases in solution. It must be recognized that CHF_2Cl is neither isosteric nor isoelectronic with methanol. It is also possible that the fluorine atoms on a molecule such as CHF_2Cl may weakly hydrogen-bond to the C−H bonds in a trialkyltriazacyclohexane.[40] Nevertheless, the similar hydrogen-bonding capabilities of CHF_2Cl and methanol suggest that methanol may be a reasonable surrogate for CHF_2Cl in an investigation of the role of hydrogen-bonding in mitigating the anomeric effect. Using the MMXTAC force field, we have performed those calculations. The results are presented in Table 4.

Docking a single methanol molecule with each trialkyltriazacyclohexane conformation at the sterically most accessible

(39) Frisch M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratman, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, Revision A.6; Gaussian, Inc.: Pittsburgh, PA, 1998.

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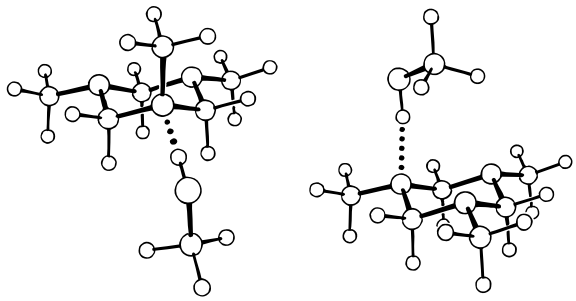
Table 4. Relative MMX Energies of Conformations of 1,3,5-Trialkyl-1,3,5-triazacyclohexanes, Hydrogen-Bonded to One Methanol Molecule, Using Modified Torsional Parameters

compound	conformation	relative energy (kcal/mol)[a]
TMTAC[b]	**eea**	0.00
	eaa	1.56
	eee	0.82
TETAC[c]	**eea**	0.00
	eaa	1.61
	eee	0.81
TPTAC[d]	**eea**	0.00
	eaa	2.03
	eee	0.70
TBTAC[e]	**eea**	0.84
	eee	0.00

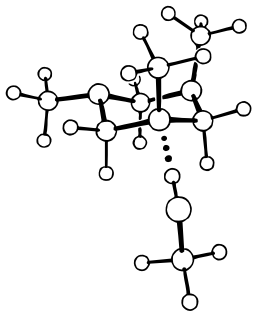
[a] Relative energy of conformation with most stable alkyl group rotamers about exocyclic N−C bonds and the most stable orientation of methanol (e.g., see structures **11**−**13**). [b] 1,3,5-Trimethyl-1,3,5-triazacyclohexane. [c] 1,3,5-Triethyl-1,3,5-triazacyclohexane. [d] 1,3,5-Tri-isopropyl-1,3,5-triazacyclohexane. [e] 1,3,5-Tri-(*tert*-butyl)-1,3,5-triazacyclohexane.

nitrogen lone pair, and optimizing the orientation of the methanol molecule, gives the relative energies listed in Table 4. For **TETAC** and **TPTAC**, the calculations employed the most stable gas-phase conformation in the array of conformations resulting from rotation about the exocyclic N−C bonds (see Table 2 and structures **3**, **7**, **8**; **6**, **9**, **10**). In Table 4, the relative energies are between the most stable complexes of each type of conformation. Illustrations of the optimized complexes for **TMTAC** are shown below (**11**−**13**). For **TETAC**, **TPTAC**,



11

12



13

and **TBTAC**, the optimized orientation of the methanol molecule with respect to the triazane ring is virtually identical to that in **TMTAC**.

For hydrogen-bonded **TMTAC**, the energy difference between **eea** and **eee** conformations is reduced to 0.82 kcal/mol (Tables 2 and 4). The energy difference between **eea** and **eaa** conformations is essentially unchanged. It is gratifying to note that these MMXTAC relative energies are in quantitative agreement with experiment. The only minor conformation of **TMTAC** detected by NMR in CHF_2Cl is the **eee** form. The **eaa** conformation apparently remains too unstable to be NMR-detectable. This speaks for the validity of the MMXTAC force field. The results for **TETAC** are essentially identical to those for **TMTAC** (Tables 2 and 4).

For **TPTAC**, the MMXTAC energy difference between hydrogen-bonded **eea** and **eee** conformations is reduced to 0.70 kcal/mol (Table 4). This energy difference would result in an NMR-detectable concentration of the **eee** conformation. While signal overlap could obscure the presence of signals due to the **eee** conformation, simulations of the DNMR spectra in 50% CF_2Cl_2/50% CHF_2Cl at 117 K and above (Figures 6 and 13S) did not require invoking the **eee** conformation (vide supra).

For **TBTAC**, the MMXTAC preference for the **eea** conformation over the **eee** form in the gas phase is 2.11 kcal/mol (Table 2). For hydrogen-bonded **TBTAC**, this preference is reversed, with **eee** more stable by 0.84 kcal/mol. The 0.84 kcal/mol preference for **eee** and the statistical preference for three monoaxial conformations would result in 95% **eee** at 105 K, in agreement with experiment.

Solvation of the trialkyltriazacyclohexanes is no doubt more complicated than the simple model used to perform these calculations. Nevertheless, the fact that these calculations are remarkably consistent with experiment supports the hypothesis that hydrogen-bonding can mitigate the anomeric effect. Preliminary calculations with three methanol molecules hydrogen-bonded to **TMTAC** also predict the **eea** conformer to be more stable than the **eee** conformer by 0.92 kcal/mol. Steric considerations suggest that **TPTAC** is accessible to solvation by no more than two methanol molecules and **TBTAC** only one. Given the fact that CHF_2Cl has a much larger molecular volume than methanol, it may be that only one CHF_2Cl molecule solvates all four trialkyltriazacyclohexanes. Solvent dielectric may also contribute to the observed changes in conformational preferences, but the experimental data suggest that this is not a major contributor (vide supra).

Experimental Section

NMR Spectra. The 250-MHz ^1H and 62.9-MHz $^{13}C\{^1H\}$ NMR spectra were recorded by using a Bruker WM-250 NMR system. The WM-250 magnet pole gap was modified to allow safe operation (no magnet O-ring freezing) down to 93 K. NMR sample temperature was varied by using a custom-built cold nitrogen gas delivery system in conjunction with the Bruker BVT-1000 temperature control unit. From about 300 down to about 200 K, temperature measurement is accurate to ±1 K. From 200 down to 100 K, the error in temperature measurement can be as high as ±3 K. The 500-MHz ^1H and 126-MHz $^{13}C\{^1H\}$ NMR spectra were recorded by using a Bruker ARX-500 NMR system. The NMR sample temperature was varied by using a Bruker BVT-2000 temperature control unit. Temperature measurement is accurate to ±3 K.

NMR samples were prepared in precision 5-mm tubes and sealed after four freeze−pump−thaw cycles. All spectra are referenced to tetramethylsilane at 0 ppm.

1,3,5-Trimethyl-1,3,5-triazacyclohexane was purchased from Aldrich Chemical Co. and used without any further purification. Purity was determined by ^1H and ^{13}C NMR spectroscopy (see text).

1,3,5-Triethyl-1,3,5-triazacyclohexane was purchased from Aldrich Chemical Co. and used without any further purification. Purity was determined by ^1H and ^{13}C NMR spectroscopy (see text).

1,3,5-Tri-isopropyl-1,3,5-triazacyclohexane was prepared as described previously by the condensation of isopropylamine with formaldehyde.[12,14,25b,41,42] Purification was done by fractional distillation

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under reduced pressure: bp 382−383 K (20 mmHg). Molecular structure and purity were determined by ^{1}H and ^{13}C NMR spectroscopy (see text).

Anal. Calcd. for $C_{12}H_{27}N_3$: C, 67.55; H, 12.76; N, 19.69. Found: C, 67.29; H, 12.76; N, 19.74.

1,3,5-Tri-(*tert*-butyl)-1,3,5-triazacyclohexane was prepared as described previously by the condensation of *tert*-butylamine with formaldehyde.[12,14,25b,41,42] Purification was done by fractional distillation under reduced pressure: bp 401−403 K (20 mmHg). Molecular structure and purity were confirmed by ^{1}H NMR (see text) and ^{13}C NMR ($CBrF_3$ at 200 K): 28.06 (methyl carbons), 54.37 (quaternary carbons), and 64.86 ppm (methylene carbons).

Anal. Calcd. for $C_{15}H_{33}N_3$: C, 70.53; H, 13.02; N, 16.45. Found: C, 70.27; H, 12.86; N, 16.46.

Acknowledgment. C.H.B. is grateful to the University of Vermont Committee on Research and Scholarship for support of this research.

Supporting Information Available: Table showing rate constants as a function of temperature for the chair-to-chair interconversion in 1,3,5-trialkyl-1,3,5-triazacyclohexanes, and figures showing experimental $^{13}C\{^{1}H\}$ DNMR spectra of 1,3,5-trimethyl-1,3,5-triazacyclohexane (10% v/v in CF_2Cl_2), 1,3,5-triethyl-1,3,5-triazacyclohexane (10% v/v in CF_2Cl_2), 1,3,5-triethyl-1,3,5-triazacyclohexane (10% v/v in 50% CF_2Cl_2/50% CHF_2Cl), and 1,3,5-tri-isopropyl-1,3,5-triazacyclohexane (10% v/v in CF_2Cl_2) and theoretical simulations, experimental ^{1}H DNMR spectra of 1,3,5-trimethyl-1,3,5-triazacyclohexane (3% v/v in CHF_2Cl), 1,3,5-trimethyl-1,3,5-triazacyclohexane (3% v/v in 50% CF_2Cl_2/50% CHF_2Cl), the methylene groups in 1,3,5-triethyl-1,3,5-triazacyclohexane (3% v/v in 50% CF_2Cl_2/50% CHF_2Cl), the methine and methylene protons in 1,3,5-tri-isopropyl-1,3,5-triazacyclohexane (3% v/v in CF_2Cl_2), the methine and methylene protons in 1,3,5-tri-isopropyl-1,3,5-triazacyclohexane (3% v/v in 50% CF_2Cl_2/50% CHF_2Cl), and due to the *tert*-butyl groups of 1,3,5-tri-(*tert*-butyl)-1,3,5-triazacyclohexane (3% v/v in 50% CF_2Cl_2/50% CHF_2Cl) and theoretical simulations, ^{1}H NMR spectra of 1,3,5-trimethyl-1,3,5-triazacyclohexane (3% v/v in CHF_2Cl) at 130 K with narrow-band homonuclear irradiation at 2.06 ppm, the methyl groups of 1,3,5-triethyl-1,3,5-triazacyclohexane (3% v/v in CF_2Cl_2) at 199 and 117 K, the methyl groups of 1,3,5-triethyl-1,3,5-triazacyclohexane (3% v/v in 50% CF_2Cl_2/50% CHF_2Cl) at 199 and 117 K, and due to the methylene protons of 1,3,5-tri-(*tert*-butyl)-1,3,5-triazacyclohexane (3% v/v in 50% CF_2Cl_2/50% CHF_2Cl) at various temperatures, and amplifications of selected regions of the experimental ^{1}H DNMR spectra of 1,3,5-trimethyl-1,3,5-triazacyclohexane (3% v/v in 50% CF_2Cl_2/50% CHF_2Cl) (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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