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Elucidating the Origin of Conformational Energy Differences in Substituted 1,3-Dioxanes: A Combined Theoretical and Experimental Study

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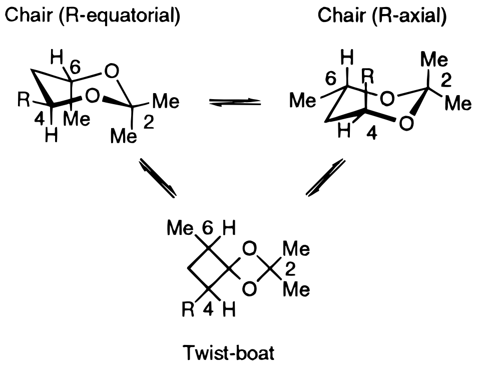
^{13}C NMR spectroscopy, *ab initio* quantum mechanics, and molecular mechanics have been used to investigate the *trans*-4-(trifluoromethyl)-2,2,6-trimethyl-1,3-dioxane chair/twist-boat equilibrium. The molecular mechanics calculations were based upon the MM3 and AMBER force fields. A 6-31G* basis set was used for the *ab initio* calculations, and MP2 correlation corrections were applied. Both the *ab initio* and AMBER molecular mechanics calculations are consistent with the ^{13}C NMR chemical shift differences for the *trans*-4-(trifluoromethyl)-2,2,6-trimethyl-1,3-dioxane conformers. The predicted chair to twist-boat equilibrium suggested by the MM3 calculations is not consistent with the experimental data. These results support the suggestion by Howard *et al.* (Howard, A. E.; Cieplak, P.; Kollman, P. A. *J. Comput. Chem.* **1995**, *16*, 243−261) on the critical role of electrostatic interactions in determining the chair/twist-boat equilibrium.

Introduction

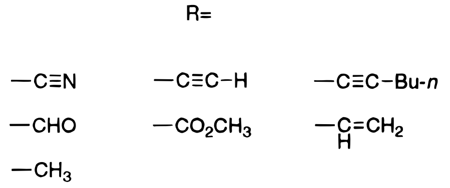
Rychnovsky and Skalitzky[2] have recently introduced a ^{13}C NMR spectroscopic method to determine the stereochemistry of 1,3-diols. *syn*-1,3-Diol-derived acetonides exist in a chair conformation with the C-4 and C-6 substituents in equatorial positions while the *anti*-1,3-diol acetonides are in an equilibrium between the chair and the twist-boat conformation (Scheme 1). ^{13}C NMR spectroscopy can distinguish between acetonide conformations based upon the chemical shifts of the C-2 methyl groups.

During the course of their investigations, Rychnovsky and co-workers[3] synthesized a series of 2,2-dimethyl-*trans*-4-substituted-6-*n*-hexyl-1,3-dioxanes in order to probe the limits of their ^{13}C NMR assignment method. The twist-boat conformation is thought to be preferred by *anti*-1,3-diol acetonides due to an alleviation of the interaction between the C-2 methyl group and the C-4 or C-6 substituent. This interaction would be present in the chair conformation. Rychnovsky and co-workers[3] wondered if they could change the conformational preference in *anti*-1,3-diol acetonides (2,2-dimethyl-*trans*-4,6-disubstituted-1,3-dioxanes) by varying the steric requirements of the C-4 substituent. They[3] determined the experimental ΔG's for the chair to twist-boat equilibrium of a series of 2,2-dimethyl-*trans*-4-substituted-6-*n*-hexyl-1,3-dioxanes where the substituents varied as shown in Scheme 2.

Scheme 1



Scheme 2



It was found that the chair conformation was preferred for the first three members of the series (C-4 = cyano, ethynyl, and 1-hexynyl) while the others showed a preference for the twist-boat conformation. Rychnovsky *et al.*[3] compared their experimental results with several computational methods. The relative energetic trend for the chair to twist-boat equilibrium was well reproduced by 3-21G, 6-31G*, and MP2/6-31G* *ab initio* quantum mechanical[4] and semiempirical AM1 methods. However, MM2* and MM3* molecular mechanics methods[5] and the semiempirical PM3 method poorly reproduced the MP2/6-31G* model and experimental trends.

Howard *et al.*[1] sought to study this 1,3-dioxane chair to twist-boat equilibrium using another molecular me-

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chanics force field in an attempt to understand the apparent failure of molecular mechanics to reproduce the conformational energies. They were able to show that a "simple" force field with electrostatic potential fit charges[6-9] did an excellent job of reproducing both the relative and absolute conformational energies. They also proposed that the physical basis for the chair to twist-boat equilibrium had two primary components: steric repulsion and electrostatic interactions. The steric repulsion component comes from the axial interaction between the methyl groups attached to C-2 and the C-4 or C-6 substituent in the chair conformation. With respect to electrostatic interactions, they proposed[1] that those substituents that can most effectively withdraw electrons from the dioxane ring would express the greatest preference for the chair conformation since their electrostatic interactions with the ring will be most favorable. Specifically, they suggested that a C-4 substituent $-CF_3$ would be an excellent probe of the importance of electrostatic effects in the chair/twist-boat equilibrium. This is because $R_4 = CH_3$ in Scheme 2 is the most "crowded" substituent and the one which has the largest preference for being in the twist-boat conformation.

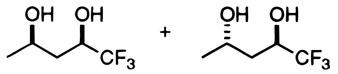
A substituent $R_4 = CF_3$ would be expected to be at least as sterically crowded as $R_4 = CH_3$, and thus, on steric grounds, it would favor the twist-boat conformation at least as much as CH_3. However, as noted by Howard *et al.*,[1] CH_3 has a polarity $C^{\delta-}H^{\delta+}$, whereas CF_3 has a polarity $C^{\delta+}F^{\delta-}$ like that of $C^{\delta+}{\equiv}N^{\delta-}$, which is the substituent that most favors the chair conformation. The relative total energies of different R_4 substituents correlate quantitatively with the relative electrostatic energy and the partial charge separation in the R_4 substituent is qualitatively consistent with the concept that the more electron withdrawing a substituent the more the partial charge at C_4 can interact with O_1 in the chair conformation.[1] Thus, this suggests the important role of electrostatics in this conformational equilibrium, although it cannot be proven given the distributed nature of electrostatic charges.

In order to provide an experimental test of this mechanistic insight offered by the study of Howard *et al.*,[1] the UCSF group proposed to S. Rychnovsky that the $R_4 = CF_3$ substituent molecule be studied in the series where R_6 = hexyl. Rychnovsky and Powers refined that concept, suggesting that the molecule with $R_4 = CF_3$, $R_6 = CH_3$, and *trans* R_4 and R_6 substituents would allow a more direct comparison of the tendencies of CH_3 and CF_3 to be in the axial position of any chair conformation that was formed. They also expected such a molecule to be more accessible synthetically. Thus, the UCSF group embarked on the *ab initio* and molecular mechanics calculations in parallel with the synthetic and NMR spectroscopic efforts of the Minnesota group.

In this paper, we detail our collaborative experimental and computational exploration of the *trans*-4-(trifluoromethyl)-2,2,6-trimethyl-1,3-dioxane chair to twist-boat equilibrium. We also describe calculations of substituted cyclohexanes that help elucidate the role of both heteroatoms and the ring substituents in determining the conformational equilibrium.

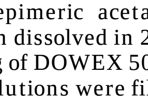
Experimental Section

Synthesis of 1,1,1-Trifluoro-2,4-pentanediol.



1,1,1-Trifluoropentane-2,4-dione (3.95 g, 25.6 mmol, 1.0 equiv) was dissolved in 50 mL of 1/1 H_2O/MeOH, and the solution was cooled to 0 °C. Sodium borohydride (958 mg, 25.6 mmol, 1.0 equiv) was added slowly to the cold solution, followed by removal of the ice bath and allowing to warm to room temperature. After stirring for 2 h, 50 mL of 1 N HCl was added and the solution was stirred for an additional 1 h. The methanol was removed under reduced pressure, and the aqueous layer was extracted (3 × EtOAc). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to give a clear colorless oil. The crude oil was dissolved in 50 mL of CH_2Cl_2 followed by the addition of benzaldehyde dimethyl acetal (3.84 mL, 25.6 mmol, 1.0 equiv) and 10 mg of $TsOH{\cdot}H_2O$. After stirring for 5 days the solution was diluted with saturated $NaHCO_3$, extracted (3 × CH_2Cl_2), dried (Na_2SO_4), and concentrated under reduced pressure. The crude colorless liquid thus obtained was purified via MPLC (SiO_2, 5% EtOAc/hexanes) to obtain two fractions containing the *anti* and *syn* protected diols (elution order: *anti* followed by *syn*) as mixtures of their epimeric acetals. The *anti* and *syn* mixtures were then each dissolved in 20 mL of MeOH followed by the addition of 10 mg of DOWEX 50W-X1 (H^+) resin. After stirring for 1 day the solutions were filtered and concentrated under reduced pressure. Purification of both the *anti*- and *syn*-containing oils by flash chromatography (SiO_2, 10% EtOAc/hexanes followed by 100% EtOAc/hexanes) gave the *anti* (845 mg, 5.34 mmol, 21%) and *syn* (1.062 g, 6.72 mmol, 26%) diols respectively as colorless oils. *anti*-1,1,1-Trifluoro-2,4-pentanediol: IR (neat) 3454, 2975, 2936, 1457, 1416, 1381, 1352, 1273, 1206, 1171, 1141, 1117, 1070, 988, 932, 821 cm^{-1}; ^1H NMR (CD_2Cl_2, 500 MHz) δ 4.23 (m, 1 H), 4.13 (m, 1 H), 3.64 (broad singlet, 2 H), 1.75 (ddd, J = 2.8, 9.8, 14.4 Hz, 1 H), 1.68 (ddd, J = 2.8, 9.5, 14.4 Hz, 1 H), 1.26 (d, J = 6.1 Hz, 3 H); ^{13}C NMR (CD_2Cl_2, 125 MHz, DEPT) CH 67.2 (q, J = 124 Hz), 63.9; CH_2 37.5; CH_3 23.3; HRMS (CI, NH_3) 176.0897 (M + NH_4^+). *syn*-1,1,1-Trifluoro-2,4-pentanediol: IR (neat) 3451, 2975, 2935, 1381, 1359, 1277, 1171, 1143, 1124, 1076, 991, 935, 822 cm^{-1}; ^1H NMR (CD_2Cl_2, 500 MHz) δ 4.25 (m, 1 H), 4.15 (m, 1 H), 3.21 (broad singlet, 2 H), 1.77 (ddd, J = 3.1, 10.0, 14.4 Hz, 1 H), 1.69 (ddd, J = 2.7, 9.2, 14.7 Hz, 1 H), 1.26 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (CD_2Cl_2, 125 MHz, DEPT) CH 67.3 (q, J = 124 Hz), 64.1; CH_2 37.4; CH_3 23.4; HRMS (CI, NH_3) 176.0893 (M + NH_4^+).

Synthesis of *cis*-4-(Trifluoromethyl)-2,2,6-trimethyl-1,3-dioxane (*cis*-2f).



syn-1,1,1-Trifluoro-2,4-pentanediol (200 mg, 1.27 mmol) was dissolved in 2 mL of dry acetone followed by the addition of 1 mg of camphorsulfonic acid. After stirring for 17 h the solution was diluted with 10 mL of CH_2Cl_2 and 20 mL of saturated $NaHCO_3$. The mixture was extracted (2 × CH_2Cl_2), dried (Na_2SO_4), and concentrated from an ice bath under reduced pressure to give a clear colorless liquid: ^1H NMR (CD_2Cl_2, 500 MHz) δ 4.28 (m, 1 H), 4.04 (m, 1 H), 1.74 (m, 1 H), 1.65 (m, 1 H), 1.45 (s, 3 H), 1.40 (s, 3 H), 1.19 (d, J = 6.1 Hz, 3 H); ^{13}C NMR (CD_2Cl_2, 125 MHz, DEPT) C 99.8; CH 68.5 (q, J = 128 Hz), 64.3; CH_2 37.9; CH_3 29.8, 22.1, 19.58; HRMS (CI, NH_3) 199.0950 (M + H^+).

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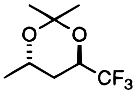
Synthesis of *trans*-4-(Trifluoromethyl)-2,2,6-trimethyl-1,3-dioxane (*trans*-2f).



anti-1,1,1-Trifluoro-2,4-pentanediol (200 mg, 1.27 mmol, 1.0 equiv) was dissolved in 3 mL of CH_2Cl_2 followed by the addition of 2-methoxypropene (243 mL, 2.54 mmol, 2.0 equiv) and 1 mg of pyridinum *p*-toluenesulfonate. The solution was stirred for 27 h followed by addition of 20 mL of saturated $NaHCO_3$. The solution was extracted (2 × CH_2Cl_2), dried (Na_2SO_4), and concentrated under reduced pressure from an ice bath to give 421 mg of a 1/1 mixture of product with 2,2-dimethoxypropane: ^1H NMR (CD_2Cl_2, 500 MHz) δ 4.20 (ddddd, $J = 6.7, 9.4, 6.8 \times 3$ Hz, 1 H), 4.02 (ddddd, $J = 5.9, 9.3, 6.3 \times 3$ Hz, 1 H), 2.02 (ddd, $J = 5.9, 9.4, 13.1$ Hz, 1 H), 1.67 (ddd, $J = 6.7, 9.3, 13.0$ Hz, 1 H), 1.40 (s, 3 H), 1.37 (s, 3 H), 1.22 (d, $J = 6.3$, 3 H); ^{13}C NMR (CD_2Cl_2, 125 MHz, DEPT) C 101.6; CH 66.0 (q, $J = 128$ Hz), 62.7; CH_2 32.9; CH_3 24.8, 24.5, 21.5; HRMS (CI, NH_3) 199.0947 ($M + H^+$).

Computational Methods

Quantum Mechanics Calculations. Quantum mechanical calculations were carried out using the Gaussian 90 software package.[4] The quantum mechanical optimizations and single-point energy calculations were performed using the 6-31G* basis set. Optimizations for compounds **2f**, **3**, and **4a**−**c** were performed during the course of this study while the results for compounds **1** and **2a**−**e** have been previously reported.[1,3] Single point MP2 correlation corrections were also made for each of these compounds. Solvent corrections (SCRF correction), using the Onsager reaction field model with a $CHCl_3$ dielectric constant of 4.8, have been calculated for the 6-31G* basis set. The optimized structures for compounds *trans*-4-(trifluoromethyl)-2,2,6-trimethyl-1,3-dioxane are available as Supporting Information.

Molecular Mechanics Calculations. Molecular mechanics calculations were performed using the AMBER 4.0 software suite[10] and the Cornell *et al.* force field.[8,9] In our previous study of 1,3-dioxanes,[1] we developed several new force field parameters, and we have again used those parameters in this study, including the torsional term: $V_1/2$ (OS−CT−OS−CT) = 1.6 kcal/mol, phase shift = 180°. The parameters for fluorine are from Gough *et al.*[11] These parameters and the charges for **2f** are listed in the Supporting Information. All nonbonded interactions were included in calculations. The 1−4 electrostatic and 1−4 van der Waals interactions were scaled by the inverse factors of 1.2 and 2, respectively.[8] The molecular mechanics calculations were performed using a constant dielectric.

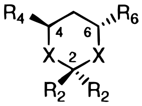
The MM3 molecular mechanics force field[12] was also used in this study. The default program options and parameters were used except for the following two parameters which were not available in the standard model and were chosen from the analogous 2−1−6(−1) parameters.

atom type	K_θ	θ_0	atom type	V_1	V_2	V_3
4 1 6	0.700	109.500	4 1 6 1	0.000	0.000	0.403

where atom type 1 = sp^3 carbon, 2 = sp^2 carbon, 4 = sp carbon, 6 = C−O−H, C−O−C, or O−O oxygen.

Point Charges Derived from Electrostatic Potential Calculations. The AMBER force field uses atom-centered point charges which are derived from electrostatic potential calculations using a 6-31G* wave function and following the methodology of Bayly *et al.*[13] The RESP method[13] uses a hyperbolic penalty function to restrain charges during the fitting process. It[13] also uses a two-stage procedure which allows one to force charge equivalence on atoms which might not be related by molecular symmetry, such as atoms that exchange during dynamic processes.

Table 1. Compounds Investigated during This Study



	1	2a	2b	2c	2d	2e	2f	3	4a	4b	4c
X	O	O	O	O	O	O	O	CH_2	CH_2	CH_2	CH_2
R_2	H	CH_3	CH_3	CH_3	CH_3	CH_3	CH_3	H	CH_3	CH_3	CH_3
R_4	H	CN	C≡CH	CHO	$CH{=}CH_2$	CH_3	CF_3	H	CN	CH_3	CF_3
R_6	H	CH_3	CH_3	CH_3	CH_3	CH_3	CH_3	H	CH_3	CH_3	CH_3

For this study, we have used a point charge set previously[1] denoted using the *respConformer* descriptor. Thus, a hyperbolic penalty function was used during the fitting process, the quantum mechanical electrostatic potentials were calculated for both the twist boat and chair (R_4 substituent axial) conformations of molecules, and both electrostatic potentials were then used to derive a common charge set for each conformer pair.

Results and Discussion

Calculation of the 4-(Trifluoromethyl)-2,2,6-trimethyl-1,3-dioxane Conformational Energies (2f). In our previous investigation,[1] we suggested that a greater percentage of **2f** (Table 1) would be found in the chair conformation than that found for **2e**. We based that prediction on the following reasoning: The increased steric demands of a axial trifluoromethyl versus a methyl group would tend to favor the twist-boat conformation. However, we expected this contribution to be smaller and outweighed by the electrostatic interactions of the C-4 substituent with the ring atoms. Both experimental[3] and computational[1,3] results show a decreased occupation of the chair conformation along the series C≡N, C≡CH, CHO, $CH{=}CH_2$, and CH_3 (**2a**−**e**). The positive partial charge on C-4 in this series is decreasing with the positive dipole closest to the ring at one extreme ($C^{\delta+}{\equiv}N^{\delta-}$) and the polarity reversed ($C^{\delta-}{-}H^{\delta+}$) for the methyl group at the other extreme. Since the trifluoromethyl charge distribution would be of opposite polarity ($C^{\delta+}{-}F^{\delta-}$) to the methyl group, the electrostatic interaction between the ring atoms (especially the oxygens) and the C-4 carbon would be expected to be more favorable and the chair conformation consequently stabilized.

The twist-boat and two chair conformations (CF_3 in the axial or equatorial position) of compound **2f** were optimized at the 6-31G* basis level. Single point MP2 correlation corrections and Onsager reaction field model solvent corrections (SCRF correction) were also determined. The optimized geometries calculated at the 6-31G* basis level were used as starting structures for AMBER and MM3 molecular mechanics calculations. Table 2 provides a comparison of the relative energies of the chair and twist-boat conformations with $R_4 = CH_3$ (**2e**) and $R_4 = CF_3$ (**2f**). As one can see, the *ab initio* calculations find that this energy difference decreases from 2.33 kcal/mol for **2e** to 1.38 kcal/mol for **2f**, consistent with our prediction. The AMBER molecular mechanics model finds this energy difference nearly identical for **2e** (1.51 kcal/mol) and **2f** (1.44 kcal/mol), whereas

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Table 2. Compounds 1, 2a,e,f, 3, and 4a−c Conformer Energies[a]

	1,3-dioxane (**1**)			*trans*-4-cyano-2,2,6-trimethyl-1,3-dioxane (**2a**) R= C≡N			*trans*-2,2,4,6-tetramethyl-1,3-dioxane (**2e**) CH_3		
	twist-boat	chair	δ*E*	twist-boat	chair	δ*E*	twist-boat	chair	δE
MP2/6-31G* total energy	−306.69204	−306.69974	4.83	−516.21812	−516.22129	1.99	−463.38937	−463.38565	−2.33
AMBER total energy	9.54	5.89	3.65	−47.33	−49.29	1.96	−68.64	−67.13	−1.51
AMBER bond-angle-dihedral	5.66	2.54	3.12	6.44	6.41	0.03	6.28	8.12	−1.84
AMBER vdw	−0.32	−0.36	0.04	−1.50	−1.48	−0.01	−1.43	−1.22	−0.21
AMBER 1−4 vdw	4.63	3.28	1.35	6.80	5.26	1.54	7.35	5.32	2.04
AMBER eel	−0.43	0.43	−0.86	−59.07	−59.51	0.44	−80.84	−79.35	−1.50
MM3 total energy	9.52	2.23	7.29	16.11	12.90	3.21	16.60	16.59	0.01
MM3 bond-angle-dihedral	6.62	−0.95	7.57	8.79	5.16	3.63	8.96	8.57	0.39
MM3 vdw	0.16	0.15	0.01	0.21	0.91	−0.70	0.31	1.12	−0.81
MM3 1−4 vdw	5.99	5.22	0.76	9.70	8.53	1.17	10.51	9.21	1.30
MM3 dipole−dipole	−3.24	−2.18	−1.06	−2.59	−1.70	−0.89	−3.19	−2.31	−0.88

	trans-4-(trifluoromethyl)-2,2,6-trimethyl-1,3-dioxane (**2f**) (CF_3)			cyclohexane (**3**)			*trans*-4-cyano-2,2,6-trimethylcyclohexane (**4a**) (R = C≡N)		
	twist-boat	chair	δ*E*	twist-boat	chair	δ*E*	twist-boat	chair	δ*E*
MP2/6-31G* total energy	−760.47326	−760.47106	−1.38	−234.98100	−234.99162	6.68	−444.49756	−444.50509	4.73
AMBER total energy	−38.59	−37.15	−1.44	10.21	3.11	7.10	5.08	−0.65	5.73
AMBER bond-angle-dihedral	7.07	10.80	−3.73	6.29	0.53	5.76	7.21	3.84	3.37
AMBER vdw	−1.65	−1.29	−0.36	−0.28	−0.52	0.24	−1.48	−1.34	−0.14
AMBER 1−4 vdw	7.70	5.67	2.03	4.18	3.08	1.10	7.87	5.94	1.93
AMBER eel	−51.70	−52.32	0.62	0.02	0.02	0.00	−8.52	−9.09	0.57
MM3 total energy	19.96	22.62	−2.66	13.80	8.04	5.76	19.70	15.16	4.53
MM3 bond-angle-dihedral	7.26	9.61	−2.35	6.97	2.19	4.78	9.33	5.19	4.15
MM3 vdw	0.15	1.00	−0.85	−0.14	−0.32	0.18	0.28	0.82	−0.54
MM3 1−4 vdw	11.12	9.67	1.45	6.97	6.17	0.80	10.08	9.15	0.93
MM3 dipole−dipole	1.43	2.34	−0.91	0.00	0.00	0.00	0.00	0.00	0.00

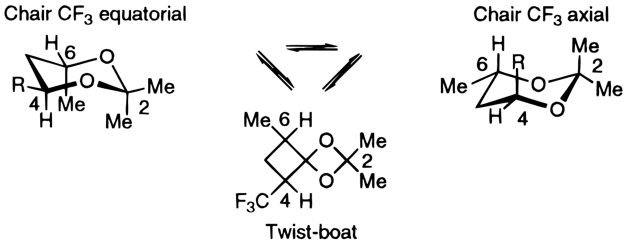
	trans-2,2,4,6-tetramethylcyclohexane (**4b**) (CH_3)			*trans*-4-(trifluoromethyl)-2,2,6-trimethylcyclohexane (**4c**) (CF_3)		
	twist-boat	chair	δ*E*	twist-boat	chair	δ*E*
MP2/6-31G* total energy	−391.65836	−391.66070	1.42			
AMBER total energy	4.50	1.18	3.32	7.95	6.54	1.41
AMBER bond-angle-dihedral	7.08	5.40	1.68	7.63	8.24	−0.61
AMBER vdw	−1.27	−0.88	−0.39	−1.19	−0.56	−0.63
AMBER 1−4 vdw	8.25	6.18	2.07	8.77	6.68	2.09
AMBER eel	−9.56	−9.52	−0.04	−7.25	−7.81	0.56
MM3 total energy	20.47	18.68	1.79			
MM3 bond-angle-dihedral	9.50	7.62	1.88			
MM3 vdw	0.62	1.38	−0.76			
MM3 1−4 vdw	10.35	9.68	0.67			
MM3 dipole−dipole	0.00	0.00	0.00			

[a] All molecular mechanics and reaction energies are expressed in kcal/mol while quantum mechanic energies for individual molecular conformations are given in units of Hartrees. In order to be consistent, we have used the same numbering system and nomemclature for the cyclohexyl compounds as for the 1,3-dioxanes.

the MM3 model finds the difference to increase from 0.01 kcal/mol (**2e**) to 2.66 kcal/mol (**2f**). Thus, the results for MM3 are, as expected, dominated by the steric effect, and the bulkier CF_3 has a greater preference for twist-boat than CH_3. The AMBER results suggest that increased steric bulk is "opposed" by the electrostatic effect in going from CH_3 to CF_3, and the *ab initio* calculations suggest the electrostatic effect plays an important role in going from CH_3 to CF_3, since the twist-boat preference is reduced by ca. 1 kcal/mol.

Until now, we have only considered the conformations of **2f** with the CF_3 group axial. What about the conformation with CF_3 equatorial, which requires CH_3 to be axial? This is a more direct measure of the relative preference of a CF_3 or a CH_3 to tolerate a more sterically demanding axial position. The results are summarized in Table 3, and both *ab initio* and AMBER calculations find, by 1.6 and 0.6 kcal/mol respectively, that it is easier to place the CF_3 axial. MM3 finds the opposite, with the CH_3 axial conformer only 0.26 kcal/mol less stable than twist-boat, but the axial CF_3 2.62 kcal/mol less stable.

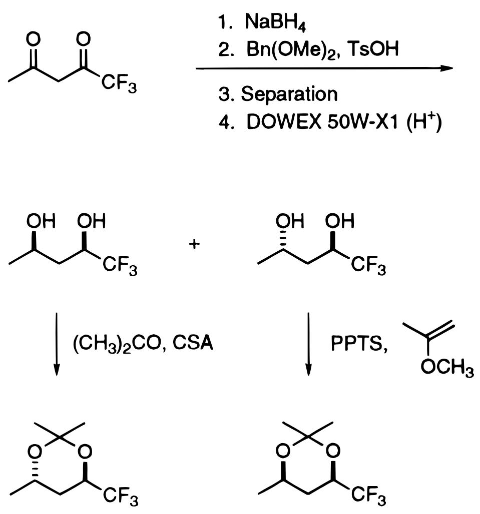
Table 3. Calculated Relative Energies for the Twist-Boat and Chair Conformations of Compound 2



	calculated energies (kcal/mol)			
	MP2/6-31G*// 6-31G*	MP2/6-31G*// 6-31G* + SCRF correction	AMBER	MM3
twist-boat	0.00	0.00	0.00	0.00
chair CF_3 axial	1.38	1.53	1.44	2.62
chair CF_3 equatorial	2.98	3.18	2.04	0.26

Both the quantum and molecular mechanical computational methods predict the twist-boat conformation to be

Scheme 3



more energetically favored than either chair conformation (Table 3). For the quantum mechanical calculations and the AMBER force field, the CF_3 axial chair conformation was found to be more stable than the CF_3 equatorial chair conformation while the reverse stability was found for the MM3 force field. This suggests that in the MM3 force field the steric bulk of the trifluoromethyl group is a more important contributor to the conformational equilibrium than the electrostatic interaction.

What is the agreement between the various computational results and our hypothesis[1] concerning the origin of the conformational preferences in these 1,3-dioxanes? In Table 2, the MP2/6-31G* and AMBER calculations both predict that replacement of a methyl group with a trifluoromethyl group in these 1,3-dioxanes will enhance the chair population, which is in agreement with our hypothesis. However, the MM3 force field calculation predicts the opposite: that the population of the twist-boat conformation will be enhanced in going from **2f** to **2e**. A reviewer of this paper has suggested that "MM3 has never been parameterized for such systems, and it seems like a cheap shot to repeatedly point out how much better AMBER is in these comparisons". Although to our knowledge there has been no report in the literature for MM3 calculations parameterizing the model for 1,3-dioxanes, the force field (MM3(89), MM3(92), and MM3-(94); see footnote in ref 1) does contain explicit torsional parameters for O−C−O−C units, and therefore, it appears that the relevant parameterization has been done.

Experimental Determination of the *trans*-4-(Trifluoromethyl)-2,2,6-trimethyl-1,3-dioxane Chair to Twist-Boat Equilibrium (*trans*-2f). The *cis* and *trans* isomers of compound **2f** were synthesized according to Scheme 3. 1,1,1-Trifluoropentane-2,4-dione was reduced with sodium borohydride, and the resulting diols were protected as benzylidine acetals. After chromatographic separation of the *syn* and *anti* protected diols, the compounds were treated with acid to regenerate the *syn*- and *anti*-1,1,1-trifluoro-2,4-pentanediol. The *cis*-1,3-dioxane **2f** was prepared by treating the *syn*-1,3-diol with acetone and camphorsulfonic acid. The thermodynamically less favorable ketalization of *anti*-1,1,1-trifluoro-2,4-pentanediol was carried out using 2-methoxypropene and pyridinum *p*-toluenesulfonate to give *trans*-**2f**.

^{13}C NMR can be used to determine the 4-substituted-2,2,6-trimethyl-1,3-dioxane ring conformation by measuring the chemical shift of the *gem*-methyl groups at C-2. In the twist-boat conformation, both methyl groups would be expected to appear at ca. 24.7 ppm.[3] The equatorial C-2 methyl group would have a chemical shift of ca. 31.0 ppm[3] in the chair conformation. The axial C-2 methyl group's chemical shift is much less certain, but can be estimated as ca. 22 ppm based on the chemical shift of the 4-cyano-2,2,6-trimethyl-1,3-dioxane that exists in a chair conformation and has an axial cyano group at the 4-position.[3]

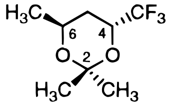
trans-4-(Trifluoromethyl)-2,2,6-trimethyl-1,3-dioxane (**2f**) was studied by ^{13}C NMR, and the chemical shifts of the C-2 *gem*-methyl groups are listed in Table 4. As shown in Table 4, the chemical shift difference between the C-2 methyl groups is only 0.35 ppm. These peaks reflect the conformational composition of the compounds. The highest chemical shift peak is assumed to be a weighted average of the twist-boat and equatorial methyl chair contributions.[3]

Using a simple Boltzmann distribution analysis, we have calculated the expected C-2 methyl chemical shifts and chemical shift differences for **2f** based upon conformational energy differences calculated by quantum mechanics and the MM3 and AMBER force fields (Table 4). Both MP2/6-31G* and AMBER are in reasonable agreement with experiment; both predict that the difference between the chemical shift of the two methyl groups should be less than 1 ppm, and the experimental value is 0.35 ppm. The experimentally observed shift difference is small, and thus, the equilibrium favors the twist-boat conformation. The precise energy difference between the twist-boat and the two chair conformations cannot be established based on the experimental chemical shift data except to say that the difference is 1 kcal/mol or greater. Both AMBER and MP2/6-31G* predict enthalpy differences of greater than 1 kcal/mol for both chair isomers, and both are consistent with the experimental results. Because the MM3 energy of **2f** in the chair conformation with CF_3 equatorial is only 0.26 kcal/mol above the twist-boat conformation, this model predicts a chemical shift difference (Table 4) of 3.4 ppm and is clearly not consistent with the experimental data.

Unfortunately, the experimental data cannot distinguish whether it is the CF_3 axial or CH_3 axial chair conformation which is ~10% populated, but the *ab initio* calculations and the AMBER molecular mechanics strongly suggest it is the CF_3 substituent which is axial; the MM3 calculations come to the opposite conclusion.

Calculation of Energy Differences between Twist-Boat and Chair Conformations of Substituted Cyclohexanes. We have postulated that the 1,3-dioxane ring conformation is determined by steric demands and electrostatic interactions of C-4 (C-6) and its substituent with the ring atoms. In order to further investigate this hypothesis, we have compared the conformational energies of methyl versus trifluoromethyl 4-substituted-2,2,6-trimethyl-1,3-dioxane. We have also compared the cyclohexyl analogs of compounds **1**, **2a**, **2e**, and **2f**. In Table 2, we list the MP2/6-31G*, MM3, and AMBER energies for the chair (axial substituent at C-4) and twist-boat conformers of the cyclohexane derivatives **3** and **4a**−**c**. We have catalogued selected energy differences between the 1,3-dioxane and cyclohexane compounds in Table 5. Relative to cyclohexane itself, which intrinsically strongly favors the chair conformation (by 6.7, 7.1, and 5.8 kcal/mol with *ab initio*, AMBER, and MM3, respectively), the substitution of 2,2,4,6-tetramethyl stabilizes the twist-boat by 5.3 kcal/mol (*ab initio*), 3.8 kcal/mol (AMBER),

Table 4. Experimental and Calculated[1] ^{13}C NMR Chemical Shifts of C-2 Methyl Groups [Me(a) and Me(b)][a]



	experimental ^{13}C NMR	MP2/6-31G*//6-31G*	MP2/6-31G*//6-31G* + SCRF correction	AMBER	MM3
Me(a)	24.48	25.22	25.11	25.10	23.70
Me(b)	24.83	24.50	24.54	24.67	27.12
Δ[Me(a)−Me(b)]	0.35	0.72	0.57	0.44	−3.43

[a] The following chemical shifts were assumed during the Boltzman calculation: Me-axial: 22 ppm; Me-equatorial: 31 ppm; Me-Twist boat: 24.7 ppm.

Table 5. Differences in Δ*E* (kcal/mol) for the Chair to Twist-Boat Equilibrium in Selected Molecules and the Qualitative Meaning of These Differences

$\Delta E_1 - \Delta E_2$	MP2/6-31G*// 6-31G*	AMBER	MM3	qualitative insight[a]
3 − **4b**	5.3	3.8	4.0	addition of four CH$_3$'s to cyclohexane stabilizes the TB
3 − **1**	1.8	3.4	−1.5	when comparing the relative preference of chair to twist-boat in cyclohexane vs 1,3-dioxane, *ab initio* qm and AMBER find the tb stabilized in 1,3-dioxane; MM3 has increased preference for chair
4b − **4a**	−3.3	−2.4	−2.7	substituting C≡N for CH$_3$ in tetra-CH$_3$-substituted cyclohexane stabilizes chair
2e − **2a**	−4.3	−3.5	−3.2	Substituting C≡N for −CH$_3$ in tetra-CH$_3$-substituted 1,3-dioxane stabilizes chair; this stabilization is greater than that for cyclohexane
2e − **2f**	−1.0	−0.1	2.7	QM finds that substituting CF$_3$ for CH$_3$ in tetra-CH$_3$-substituted 1,3-dioxane stabilizes chair; this stabilization is less than that seen for the C≡N substitution; AMBER shows little preference and MM3 shows a stabilization of tb

[a] Abbreviations: TB = twist-boat; QM = quantum mechanics.

and 4.0 kcal/mol (MM3). Interestingly, comparing cyclohexane to 1,3-dioxane, both *ab initio* (1.8 kcal/mol) and AMBER (3.4 kcal/mol) find that the latter molecule has a reduced preference for chair versus twist-boat whereas for MM3, dioxane has an increased preference (5.8 kcal/mol cyclohexane; 7.3 kcal/mol 1,3-dioxane).

The following trends are seen (Table 5) for the C≡N versus CH$_3$: The substitution of C≡N for CH$_3$ (**4b** → **4a**) stabilizes the cyclohexyl chair conformer over the twist-boat, and this stabilization is even greater in the corresponding 1,3-dioxane compounds (**2e** → **2a**). The nitrile group does not impose a large steric constraint. When in the axial position, the nitrile group withdraws electron density from C-4 and the electrostatic interaction of C-4 with the ring is increased. This electrostatic stabilization would be expected to be intensified when two ring carbons are substituted by oxygens, as indicated by the MP2/6-31G* calculations and AMBER where **2e** − **2a** are about 1 kcal/mol more negative than **4b** − **4a**. MM3 suggests a similar trend, albeit of smaller magnitude (ca. 0.5 kcal/mol). If **2e** is instead modified by replacing the CH$_3$ group by CF$_3$ (**2f**), the chair conformer is again stabilized, but by less than with the nitrile substituent. This trend may be rationalized by noting that the larger size of CF$_3$ versus CH$_3$ would destabilize the chair conformation since the axial CF$_3$ would experience steric repulsion with the C-2 *gem*-methyl groups.

Conclusion

This investigation has illustrated the synergy of combined experimental/theoretical studies for elucidating the conformational equilibrium of simple organic molecules. The use of both reasonably high level *ab initio* and molecular mechanical methods are complementary in that regard. The role of the former can be viewed as providing an essential and accurate reference point for the less physically correct molecular mechanics models. When there is agreement, the molecular mechanics calculations can provide useful mechanistic insight as illustrated by the suggestion[1] that the dioxanes with R$_4$ = CF$_3$ would be of interest.

It is hard to overestimate the role and importance of the MM2 and MM3 force fields in providing useful insights and understanding of the structure and conformations of organic molecules. What lessons can one take from the failure of MM3 in reproducing the relative energies of these substituted dioxanes? Historical perspective may be in order here—a key insight in the development of MM2 was Allinger's realization[14] of the importance of lower order Fourier components in determining the torsional energies of hydrocarbons. This has led to the use of multiple torsional components in MM2 and MM3 in many of the I−J−K−L atom types. Because in 1977 there was no proven useful and more accurate way to describe electrostatic contributions to conformational energies than a simple point−dipole model, most of the conformational energy differences were incorporated into the torsional term.[14]

We have taken another approach, aided by the fact that an accurate way to describe electrostatic energies was available when we began our force field development.[6,7,9,13,15] A minimalist philosophy to adding torsional potentials has been a significant difference between our approach and that in MM2 and MM3. Of course, torsional potentials should (must) be used for intrinsically quantum mechanical electronic structure effects such as the rotational barrier in ethane, but in our approach, they have been used conservatively.

It is practically a cliché in the literature that one should not overinterpret molecular mechanical energy components, given that they are less meaningful than the total energy. This is because different force fields involve more subjectivity/difference in the energy com-

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(14) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127.
(15) Singh, U. C.; Kollman, P. A. *J. Comput. Chem.* **1984**, *5*, 129−145.

ponents than the total energy which they vary in order to ensure agreement with a set of reference data. However, within our approach to parameter development we have attempted to decouple the components as much as possible. This has enabled the mechanistic insights of ref 1 and has led to the work described in this paper.

In our opinion, there are important roles for both "philosophies" of force field development. The MM2/MM3 models, which attempt to deal very accurately with even the most strained organic molecule and to derive all structural parameters to experimental accuracy, have a role in more accurate representation of more organic molecules. This approach attempts to refine all the molecular mechanical parameters with a large collection of test molecules. However, even within this philosophy, our calculations have suggested a need for a more accurate electrostatic model, although it is difficult to prove that one could not create torsional potentials to achieve the same aim.

This study has, however, further supported the usefulness of a minimalist approach to force field development in which the electrostatic model has been derived using quantum mechanical calculations, the van der Waals parameters from liquid simulations and the torsional potentials mainly derived by fitting the simplest member of given functional groups and using this torsional term for all fragments involving this group. For example, a simple V_3 Fourier term has been used to reproduce the rotational barrier in ethane and is the only term included for all I−C−C−L torsions except those where both I and L are oxygen atoms.[9] Because this approach separately derives electrostatic, van der Waals, and torsional potentials, albeit in some cases such as the peptide ϕ and ψ the torsional potentials still compensate for inaccuracies in the other parameters,[9] there is a better chance that the individual components are meaningful and that mechanistic insight can be derived using them.

The study presented here can be viewed as a proof of concept for the usefulness of this view of molecular mechanics force fields.

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Supporting Information Available: NMR spectra of *cis*- and *trans*-**2f** and **z** matrix for *trans*-**2f** in the chair conformation with CH_3 axial, chair conformation with CF_3 axial, and twist-boat conformation, optimized at the 6-31G* level (10 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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