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Chair and Twist-Boat Conformations of 1,3-Dioxanes: Limitations of Molecular Mechanics Force Fields

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The chair to twist-boat equilibrium was evaluated for a variety of *trans*-4,6-dialkyl-2,2-dimethyl-1,3-dioxanes using ^{13}C NMR spectroscopy, and these equilibrium constants were used to determine ΔG, ΔH, and ΔS for the reactions. These conformational equilibria were further evaluated using molecular mechanics, semiempirical, and ab initio calculations. Neither MM2 nor MM3 force fields accurately predict the conformational energies of these simple 1,3-dioxanes. The semiempirical method AM1 performs better than PM3, but reasonable agreement with experiment is only found upon going to ab initio methods using a 6-31G* basis set. These results illustrate that caution should be used when applying current molecular mechanics force fields to carbohydrates and other compounds containing acetal carbons. The *trans*-4,6-dialkyl-2,2-dimethyl-1,3-dioxanes are finely balanced between chair and twist-boat conformations and provide a sensitive and challenging test of the performance of computational methods.

Many natural products contain 1,3-diols, and determining the stereochemistry of these diols and polyols can be challenging. We recently introduced a method for determining the relative stereochemistry of 1,3-diols by analysis of the corresponding acetonide ^{13}C spectra.[2] It was found that syn 1,3-diol acetonides have ^{13}C methyl shifts at ca. 19 and 30 ppm, while anti 1,3-diol acetonides have ^{13}C methyl shifts at ca. 25 ppm. This empirically derived correlation has its foundation in an underlying conformational change: syn 1,3-diol acetonides adopt chair conformations while anti 1,3-diol acetonides 1 adopt 2,5-twist-boat conformations, Figure 1. The twist-boat conformation is favored because 1,3-diaxial interactions between the alkyl group at C(4) or C(6) and the C(2) methyl group destabilize both of the possible chair conformations. How large must a C(4) alkyl substituent be to destabilize the chair conformation? For instance, is an alkyne large enough to force an anti 1,3-diol acetonide to adopt a twist-boat conformation, or will it exist as a chair? Answers to these questions will help to establish the limits of the ^{13}C acetonide method for determining stereochemistry. We have investigated these questions using both computational and experimental methods, and the results shed light both on the limits of the ^{13}C acetonide method and on the limits of existing computational methods.

The conformations of 1,3-dioxanes have been a subject of investigation for more than 25 years.[3] Most 1,3-dioxanes adopt chair conformations, but a small number of substituted 1,3-dioxanes have severe steric interactions that destabilize the chair conformations and instead adopt a twist-boat conformation. The presence of nonchair conformers can be observed in the proton NMR spectrum, where the sum of the coupling constants $J_{4,5}$ and $J_{4,5'}$ is ca. 11 Hz for a chair conformer and ca. 15 Hz for a twist conformer.[4] Based on this criterion, *trans*-2,2,4,6-tetramethyl-1,3-dioxane, 1 (R_1, R_2 = CH_3), adopts a 2,5-twist-boat conformation as shown in Figure 1.[5] The enthalpy difference between the 2,5-twist-boat and chair conformation of 1 (R_1, R_2 = CH_3) has been estimated as 7.1 kcal/mol from heat of combustion data,[6] although this value is probably too large, vide infra. Chair and twist-boat conformations of 1,3-dioxanes have also been investigated by ^{13}C NMR spectroscopy.[7] Pihlaja concludes that 1,3-dioxane 1 (R_1, R_2 = CH_3) exists in a 2,5-twist-boat conformation based on the ^{13}C chemical shifts of the ring carbons. Independent evidence is available from X-ray crystal structure data. A search of the Cambridge Crystallographic Database found three examples of *trans*-4,6-dialkyl-2,2-dimethyl-1,3-dioxanes, each bearing a C(5) methyl group.[8] These three compounds, as well as a single example without the C(5) methyl group,[9] exist in a 2,5-twist-boat conformation. The structures of two of these trans 1,3-dioxanes, compounds 2 and 3, are reproduced in Figure 2. Both the NMR and X-ray data confirm that the 2,5-twist-boat conformation is energetically favored over the chair conformation for typical *trans*-4,6-dialkyl-2,2-dimethyl-1,3-dioxanes.

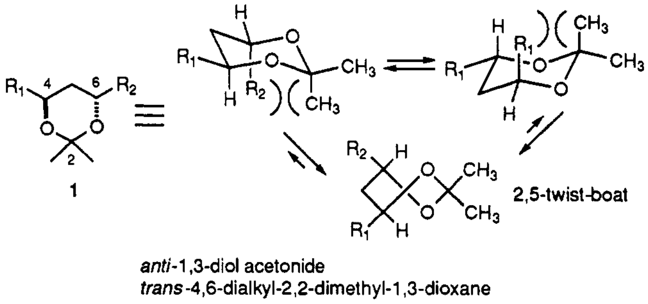

Figure 1. Chair and 2,5-twist-boat equilibrium of anti 1,3-diol acetonide 1.

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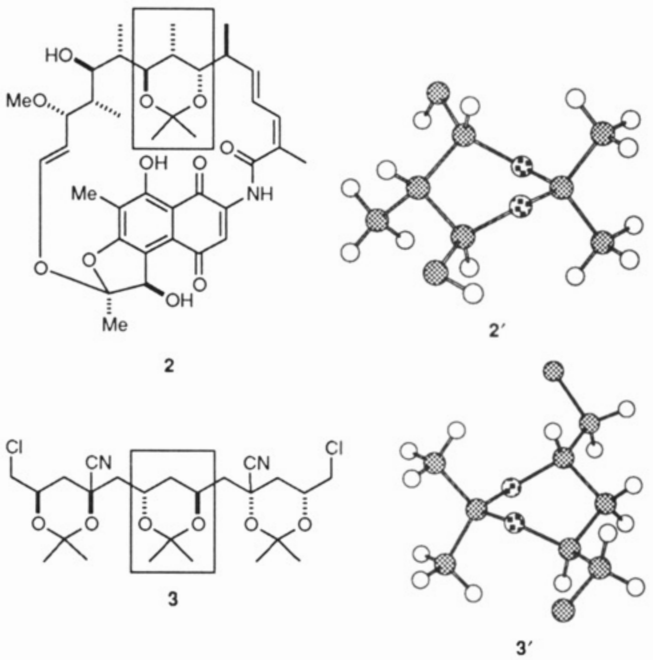
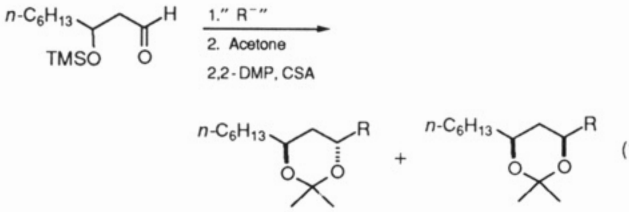


Figure 2. Conformation of anti 1,3-diol acetonides **2** and **3** from the X-ray structures. Partial structures **2′** and **3′** are shown for clarity. The complete structure of **3** is given in the supplementary material.

Conformational Behavior of 1,3-Dioxanes Studied by ^{13}C NMR. A variety of cis and trans 4,6-dialkyl-2,2-dimethyl-1,3-dioxanes were prepared, and their conformational behavior was studied by ^{13}C NMR. The 1,3-dioxanes were prepared by adding the appropriate carbon nucleophile to 3-((trimethylsilyl)oxy)nonanal[10] to give a 1,3-diol that was subsequently treated with acetone, 2,2-dimethoxypropane, and CSA to give the 1,3-dioxane (eq 1).[11] The trans isomer **4** and cis isomer **5**, or their precursor anti and syn monosilyl diols, were separated by chromatography. The aldehydes **4d** and **5d** were prepared by ozonolysis of the alkenes **4f** and **5f**. The methyl esters **4e** and **5e** were prepared by oxidative cleavage of the alkenes **4f** and **5f** followed by esterification. Carbon-13 NMR data for the C(2) methyl groups and the C(2) acetal carbon are given in Table I.[11]

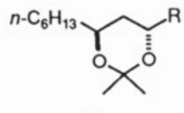


(1)

4 **5**

The ^{13}C NMR positions of the two C(2) methyl groups are very sensitive probes of the 1,3-dioxane ring conformation, with a chair conformer showing an axial methyl at ca. 19 ppm and an equatorial methyl at ca. 30 ppm while a twist-boat conformation has both methyl signals at ca. 25 ppm. We assumed that the chemical shift of the larger ppm methyl group was just a weighted average of the equatorial methyl in the chair form and one of the two nearly equivalent methyl groups in the twist-boat form and furthermore that a pure equatorial methyl had a chemical shift of 30.89 ppm and a pure twist-boat methyl had a chemical shift of 24.70 ppm.[12] These assumptions and the chemical shifts listed in Table I were used to calculate the free energy for the chair to twist-boat equilibrium shown in Table II. The larger ppm methyl group was selected because its chemical shift changes significantly between the two conformations and it is further removed and presumably less sensitive than the smaller ppm methyl group to steric perturbations caused by the different substituents. Two sources of error creep

Table I. ^{13}C Chemical Shifts of the C(2) Acetal Carbon and Methyl Groups of 1,3-Dioxanes 4 and 5[a]



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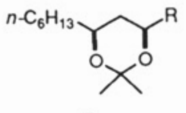

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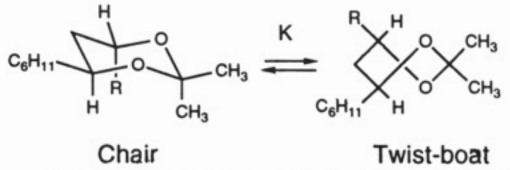
	trans (anti) 4			cis (syn) 5		
compd R =	low Me	high Me	acetal	low Me	high Me	acetal
a, CN	21.76	29.71	100.76	19.15	29.61	99.92
b, CCH	23.53	28.46	100.34			
c, CCBu^n	23.63	28.11	99.93	19.38	30.21	98.72
d, CHO	23.71	27.23	100.10	19.45	29.82	98.98
e, CO_2CH_3	23.61	26.17	100.65	19.37	29.93	99.19
f, $CH{=}CH_2$	24.68	25.42	100.18	19.96	30.42	98.66
g, CH_3	24.85	25.00	99.98	19.81	30.33	98.29

[a] Spectra recorded in $CDCl_3$; the central $CDCl_3$ peak was set to 77.00 ppm.

Table II. ΔG, ΔH, and ΔS of the Chair to Twist-Boat Equilibrium of Trans 1,3-Dioxane 4 by ^{13}C NMR[a]



	trans (anti) 1				
compd R =	K (25 °C)[b]	ΔG (25 °C)[b]	ΔH[c]	ΔS(e.u.)[c,d]	ΔG (25 °C)[c]
a, CN	0.24	0.85	0.76	−0.47	0.89
b, CCH	0.64	0.26			
c, CCBu^n	0.81	0.12	0.15	−0.48	0.29
d, CHO	1.44	−0.42			
e, CO_2CH_3	3.64	−0.77	−0.35	0.93	−0.62
f, $CH{=}CH_2$	7.64	−1.20			
g, CH_3	19.6	−1.76			

[a] ΔG and ΔH values are given in kcal/mol. The equilibrium constant K was calculated using the larger ppm methyl shift from Table I: $K = (30.89 - \text{methyl})/(\text{methyl} - 24.70)$. [b] Measured in $CDCl_3$. [c] Measured in CD_2Cl_2. [d] Entropy was calculated from ΔH and ΔG (25 °C) and was consistent with the Arrhenius intercept.

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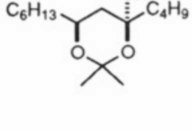
[9] Rychnovsky, S. D.; Griesgraber, G.; Britton, D. Unpublished results. The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK. The complete three-dimensional structure of compound **3** is given in the supplementary material.

[10] Prepared from heptanal: (a) $LiOC(OEt){=}CH_2$, THF, −78 °C; (b) (i) $TMSNMe_2$, (ii) DIBAL-H.

[11] Complete spectral data for each new compound are reported in the supplementary material.

[12] The twist-boat ^{13}C methyl shift of 24.7 ppm is the average of methyl shift of simple trans 4,6-dialkyl-2,2-dimethyl-1,3-dioxanes (class I, ref 2c). The equatorial ^{13}C methyl shift of 30.98 was taken from the nitrile shown below. These nitriles adopt a chair conformation (ref 7c) as can be seen in the crystal structure of compound **3**.



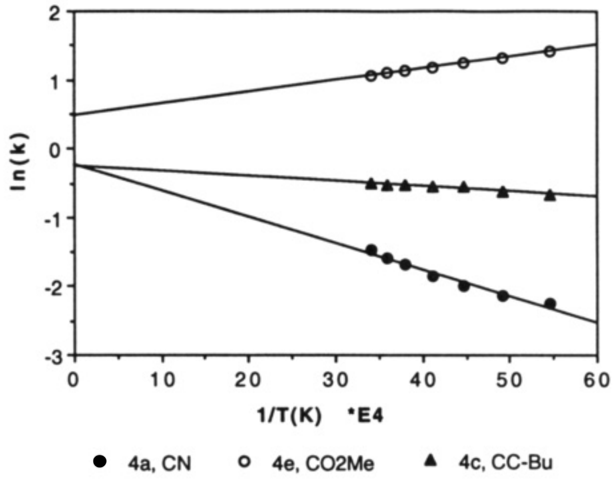
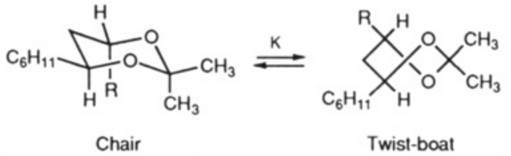


Figure 3. Van't Hoff plots for the trans 1,3-dioxanes **4a**, **4c**, and **4e** from variable-temperature NMR data in CD_2Cl_2.[13] The derived ΔG, ΔH, and ΔS are listed in Table II. The R^2 values for the linear least squares fit are 0.97, 0.92, and 0.99 respectively.

into these free energy measurements. First, it was assumed that only one of the two chair conformers was significantly populated, which is a good assumption with small substituents but a poor assumption with compounds **4f** and **4g**. Second, the estimated chemical shifts for the pure chair or the pure twist-boat conformations of **4a**–**g** maybe in error. A ±0.5 ppm uncertainty in these values leads to the asymmetric uncertainties plotted in Figure 5. The uncertainties in conformational free energies of **4a**–**e** are relatively small, whereas those for **4f** and **4g** are relatively large.

Three of the trans 1,3-dioxanes, the nitrile **4a**, the alkyne **4c**, and the methyl ester **4e**, were further evaluated by variable-temperature NMR in CD_2Cl_2.[13] The larger ppm methyl group was again used to quantify the position of equilibrium; Van't Hoff plots for each compound are shown in Figure 3, and the enthalpy and entropy of reaction are listed in Table II. The chair to twist-boat reactions show a small negative entropy for substituents such as a nitrile where rotation is not important and a small positive entropy for substituents such as an ester where rotation is important.[14] In each case the experimental entropy is small (<0.3 kcal/mol at 25 °C), and the enthalpy term dominates the free energy.

Table III. Calculated ΔH for the Chair to Twist-Boat Equilibrium of Trans 1,3-Dioxanes 6 in kcal/mol[a]



compound R =	**6a** CN	**6b** CCH	**6d** CHO	**6e** CO_2CH_3	**6f** $CH{=}CH_2$	**6g** CH_3
MM2	0.42	2.40	2.48	1.68	1.59	−1.74
MM3	3.14	3.88	2.78	2.70	3.04	0.10
PM3	2.92	2.63	1.67	1.59	1.36	2.35
AM1	2.14	2.00	0.97	1.53	0.04	−0.34
AM1+ZPE[b]	1.86	1.74	0.54	1.26	−0.31	−0.69
3-21G	2.26	2.72	0.65[c]	–	−0.50	−1.88
3-21G+ZPE[b]	2.15	2.45	0.37[c]	–	−0.82	−2.01
6-31G*	1.43	0.89	0.13	–	−1.72	−2.69
6-31G*+ZPE[b]	1.31[d]	0.62[d]	−0.13	–	−2.05[d]	−2.79
MP2	1.99	1.47	0.99	–	−0.79	−2.59
MP2+ZPE[b]	1.87[d]	1.20[d]	0.73[d]	–	−1.11[d]	−2.72[d]
exptl ΔG (**4**)	0.85	0.26	−0.22	−0.77	−1.2	−1.8

[a] In each case the energy was evaluated at the minima for the indicated method, with the exception of MP2(FC)/6-31G* energies which were evaluated at the 6-31G* minima. Energies for semiempirical and ab initio calculations are given in Table V. [b] Zero point energies (ZPE) were calculated using the computational method specified; 3-21G and 6-31G* ZPE's were scaled by 0.9. [c] The aldehyde boat conformation rather than the twist-boat conformation is a minima at 3-21G. [d] The 3-21G zero-point energy correction was used in this case.

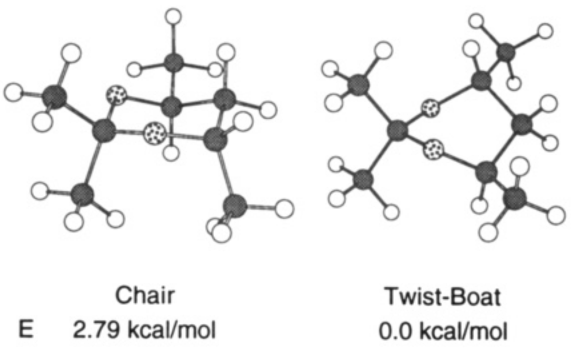


Figure 4. Chair and 2,5-twist-boat conformations of trans 1,3-dioxane **6g** at 6-31G*//6-31G*.

Nitrile **4a** is the only 1,3-dioxane in the present study that clearly favors a chair conformation. The ^{1}H NMR coupling constants in **4a**, $J_{4,5} = 2.48$ Hz, $J_{4,5'} = 6.31$ Hz, are consistent with a chair conformation and are anomalous in this series of *trans*-4,6-dialkyl-2,2-dimethyl-1,3-dioxanes.[15] The difference between the nitrile **4a** and the isosteric alkynes **4b** and **4c** may be due to anomeric stabilization of the nitrile in the chair conformation.[16] The alkyne and aldehyde dioxanes (**4b**–**d**) all show intermediate ^{13}C methyl shifts between those expected for the chair and the twist-boat conformation, implying that there is little energetic difference between the two conformations. The ester, alkene, and alkyldioxanes (**4e**–**g**) all clearly favor the twist-boat conformation.

Conformational Behavior of 1,3-Dioxanes Studied by Computation.[17] Molecular mechanics is frequently used to predict the relative energy of two conformational isomers, and force fields such as MM2 nicely reproduce cyclohexane *A* values. Predicting the equilibrium between chair and twist-boat conformations is more difficult because relatively little data on twist-boat conformations have been available to parameterize the force fields.

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(13) The ^{13}C NMR spectrum for each compound was taken at 20, 5, −10, −30, −50, −70, and −90 °C in CD_2Cl_2. Due to small chemical shift changes of the reference compounds on going to CD_2Cl_2, the formula used to calculate K in CD_2Cl_2 was $K = (31.07 - \text{methyl})/(\text{methyl } 24.70)$.

(14) Where $R_1 \approx R_2$ in Figure 1, the two chair conformations are of similar energy so an additional entropic factor of $R \ln 2 = 1.37$ eu is added to the chair conformation to correct for the presence of two states. This effect will lower the entropy of reaction. Compound **6g** has a symmetry number of 2, but it is being used to model the *enthalpy* of compound **4g** which has a symmetry number of 1, so no entropy correction was applied.

(15) The predicted coupling constants for the chair conformation (MM2) are $J_{4,5} = 1.0$ Hz, $J_{4,5'} = 6.3$ Hz. Haasnoot, C. A. G.; DeLeeuw, F. A. A. M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783–2792.

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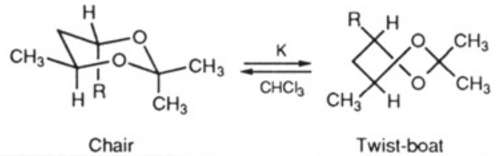
(17) Molecular mechanics calculations were carried out using Macromodel 3.5 (Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440–467). Semiempirical and ab initio calculations were carried out using either SPARTAN version 2.0 (Wavefunction Inc., 18401 Von Karman, #210, Irvine, CA 92715) or Gaussian 92 (Frisch, M. J.; Trucks, G. W.; Head-Gordon, M.; Gill, P. M. W.; Wong, M. W.; Foresman, J. B.; Johnson, B. G.; Schlegel, H. B.; Robb, M. A.; Replogle, E. S.; Gomperts, R.; Andres, J. L.; Raghavachari, K.; Binkley, J. S.; Gonzales, C.; Martin, R. L.; Fox, D. J.; Defrees, D. J.; Baker, J.; Stewart, J. J. P.; Pople, G. A. Gaussian Inc., Pittsburgh, PA, 1992).

Table IV. Calculated ΔH for the Chair to Twist-Boat Equilibrium of Trans 1,3-dioxanes 6 in $CHCl_3$ (kcal/mol)[a]



compd R =	**6a** CN	**6b** CCH	**6d** CHO	**6e** CO_2CH_3	**6f** $CH{=}CH_2$	**6g** CH_3
MM2	0.42	2.40	2.48	1.68	1.68	−1.74
MM2 ($CHCl_3$)	−0.13	1.76	2.22	1.58	0.97	−1.80
6-31G*[b]	1.31	0.62	−0.13		−2.05	−2.79
6-31G*[b] ($CHCl_3$)	0.64	0.74	−0.41		−1.91	−2.62
exptl ΔG (4)	0.85	0.26	−0.22	−0.77	−1.2	−1.8

[a] Solvent corrections for MM2 use Still's GB/SA solvation model is implemented in Macromodel 3.5. Solvent corrections for 6-31G* use the Onsager reaction field model as implemented by Gaussian 92. The MM2 structures were reminimized in the solvation calculation, while the 6-31G* energies were evaluated at the unsolvated minima. [b] 6-31G* includes correction for zero point energy. Energies for ab initio calculations are given in Table V.

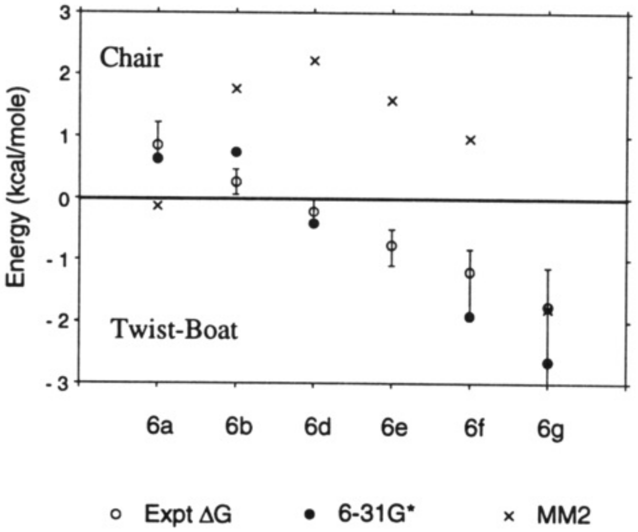


Figure 5. Comparison of the calculated conformational ΔH's of dioxanes **6**, including solvation, with the experimental ΔG's for the chair to twist-boat equilibrium of dioxanes **4** (Table IV).

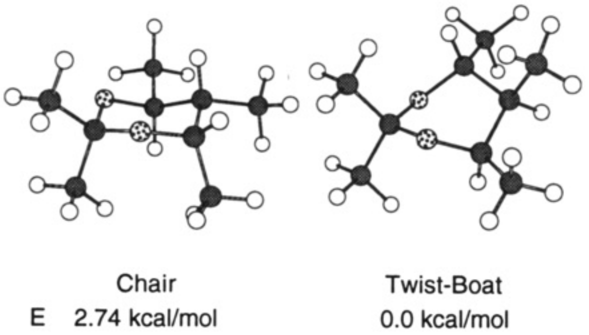


Figure 6. Chair and 2,5-twist-boat conformations of *trans*-2,2,4,5,6-pentamethyl-1,3-dioxane, **7**, at 6-31G*//6-31G*.

Conformational analysis of 1,3-dioxanes **4** is further complicated by an anomeric effect at the acetal linkage. Effective modeling of acetal linkages is important in the conformational analysis of disaccharides and higher oligosaccharides.[18] Previous molecular mechanics calculations predicted that the chair form of trans 1,3-dioxane **4** ($R_1, R_2 = CH_3$) was more stable than the twist-boat form by 0.19 kcal/mol, although this is at odds with the experimental data (vide supra).[19] Ab initio, semiempirical, and molecular mechanics methods have been used to study the conformation of carbohydrates and alicyclic compounds.[20] We have carried out conformational analyses on 1,3-dioxanes **4** using ab initio, semiempirical, and molecular mechanics methods and evaluated the results against our experimental data.

A variety of computational methods were used to predict the chair to twist-boat enthalpy of reaction for several trans 1,3-dioxanes **6a–f**, and the results are shown in Table III. In each case the C(6) *n*-hexyl substituent in **4** was replaced by a methyl substituent in **6** to reduce computational time. Multiple C(4)–R rotamers were evaluated through the 3-21G level, and in each case the low energy rotamer for the chair and twist-boat conformations is reported. Only the 3-21G low energy rotamers were evaluated at higher levels. The structures were optimized at each level except MP2/6-31G*, which were evaluated at the 6-31G* minima. Zero point energy (ZPE) corrections for all compounds were calculated at AM1 and 3-21G minima.[21] ZPE corrections for **6d** and **6g** were evaluated at the 6-31G* minima, and did not differ significantly from the 3-21G corrections, Table V.[21]

The experimental preference for the twist-boat conformation increases from left to right across Table III, but the preference calculated using MM2[22] clearly does not. MM2 predicts that aldehyde **6d** will show the largest chair preference, followed by alkyne **6b**, ester **6e**, alkene **6f**, nitrile **6a**, and finally methyl-substituted **6g**. Experimentally, the nitrile **6a** has the largest chair preference, and neither the ordering nor the MM2 energies (with the exception **6g**) are reliable. The MM3 force field[22] has been very successful in reproducing the conformational surfaces of hydrocarbons[23] but fails with these 1,3-dioxanes. The predicted chair preference now falls in the order alkyne, nitrile, alkene, aldehyde, ester, and alkyl, but in each case the chair is predicted to be the most stable conformer! The performance of both MM2 and MM3 depends on the quality of the parameters, and the parameters for α-alkoxy functional groups in compounds **6a–e** may not be appropriate for these compounds. The semiempirical method PM3 is less than successful in that it also predicts that the chair conformer will be favored in every case, and the order for chair preference is now nitrile, alkyne, alkyl, aldehyde, ester, alkene. The semiempirical method AM1 gives better results with nearly the correct ordering of functional groups, but the chair conformation is still unreasonably favored even after adding in the ZPE correction. The ab initio methods give better predictions for the enthalpy of reaction, but the 3-21G basis set reverses the ordering of alkyne and nitrile. The 6-31G* basis set does very well reproducing the correct ordering of substituents and gives very reasonable energies, especially after adding in the

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(21) The 3-21G and 6-31G* ZPE were scaled by 0.9.

(22) Macromodel 3.5 implementation of the MM2 and MM3 force fields was used throughout this work. Allinger's MM3 gives similar results: the chair preference for **6g** was 0.25 kcal/mol using Allinger's program vs 0.10 kcal/mol using Macromodel. We thank Dr. Martin Saunders at Yale University for sharing these results with us.

(23) For example, see: Anet, F. A. L.; Freedberg, D. I.; Storer, J. W.; Houk, K. N. *J. Am. Chem. Soc.* **1992**, *114*, 10969–10971.

Table V. Ab Initio and Semiempirical Energies for Chair and Twist-Boat Conformations of Trans 1,3-Dioxanes 6 and 7[a]

compd	AM1	PM3	3-21G //3-21G	6-31G* //6-31G*	MP2/6-31G* //6-31G*	6-31G* ($CHCl_3$) //6-31G*	ZPE 3-21G	ZPE 6-31G*
6a, CN								
chair	−71.65	−63.26	−511.832617	−514.680223	−516.221286	−514.681155	137.71	[b]
twist-boat	−69.51	−60.34	−511.82901	−514.677941	−516.218115	−514.679941	137.58	[b]
6b, CCH								
chair	−47.47	−46.5	−495.869051	−498.618462	−500.129997	−498.618714	145.24	[b]
twist-boat	−45.47	−43.87	−495.864716	−498.617045	−500.127651	−498.617126	144.94	[b]
6d, CHO								
chair	−134.79	−131.74	−532.704282	−535.673921	−537.237242	−535.674008	144.61	145.24
twist-boat	−132.82	−130.07	−532.703248	−535.67372	−537.235672	−535.674262	144.3	144.96
6e, CO_2CH_3								
chair	−186.84	−179.26	[b]	[b]	[b]	[b]	[b]	[b]
twist-boat	−185.32	−177.67	[b]	[b]	[b]	[b]	[b]	[b]
6f, $CH{=}CH_2$								
chair	−85.45	−81.03	−497.06843	−499.826493	−501.346556	−499.826786	160.81	[b]
twist-boat	−85.41	−79.67	−497.069224	−499.829236	−501.347807	−499.829307	160.45	[b]
6g, CH_3								
chair	−111.27	−108.23	−459.438497	−461.984964	−463.385653	−461.985301	157.15	157.56
twist-boat	−111.61	−105.88	−459.441496	−461.989247	−463.389783	−461.989322	157.01	157.45
7								
chair	[b]	[b]	−498.257734	−501.017272	[b]	[b]	[b]	[b]
twist-boat	[b]	[b]	−498.261502	−501.021638	[b]	[b]	[b]	[b]

[a] Ab initio energies are given in hartrees. Semiempirical energies and zero point energies are given in kcal/mol. Zero point energies are not corrected. [b] Not calculated.

ZPE correction. The 6-31G*-minimized structures for the chair and twist-boat conformations of the methyl-substituted **6g** are given in Figure 4. The MP2/6-31G* values do not agree with the experimental data as well as the simple 6-31G* calculations, but this may result from the MP2 energies being evaluated at the 6-31G* minima rather than the true minima for the method. These comparisons of experimental free energies with calculated enthalpies are only valid when the change in entropy is close to zero. Previous workers have found that the change in entropy between the chair and twist-boat conformations of 4 (R_1, R_2 = CH_3) is approximately zero,[5a,c] and the experimentally determined change in entropies for 1,3-dioxanes **4a**, **4c**, and **4e** are all small (<0.3 kcal/mol at 25 °C). The enthalpy term dominates the free energy in these conformational equilibria, so no computational entropy correction was attempted. Neither MM2 nor MM3 give reasonable predictions for the conformation of the 1,3-dioxanes **6**, and the best results were found using 6-31G*/6-31G* calculations with zero-point energy corrections.

Solvation can be an important factor in conformational equilibrium.[24] The enthalpies for dioxanes **6** were recalculated using Still's GB/SA solvation model for $CHCl_3$ with the MM2 force field.[25] Chloroform solvation was also incorporated into the ab initio calculations using Onsager's reaction field model[26] as implemented in Gaussian 92, and both results are given in Table IV and Figure 5. The solvation corrections for the 6-31G* calculations lead to a modest improvement in accuracy, with the largest correction applied to the relatively polar nitrile **6a**. The MM2 solvation corrections also leads to better correlation with experiment, but it still does not give the correct ordering of substituents or realistic energies.

Many 1,3-diols are present in polypropionate natural products that have a 2-methyl substituent. We used 6-31G* ab initio calculations without ZPE's to predict the structure and conformational energies of the corresponding anti acetonide, *trans*-4,6-dialkyl-2,2,5-trimethyl-1,3-dioxane, using methyl groups to model the C(4) and C(6) substituents. A slightly distorted twist-boat conformation of 1,3-dioxane **7** was found to be 2.74 kcal/mol more stable than the corresponding chair conformation, Figure 6. The 5-methyl substituent removes the C_2 symmetry of the twist-boat conformation but does not significantly change the twist-boat vs. chair equilibrium.

Conclusions

Typical *trans*-4,6-dialkyl-2,2-dimethyl-1,3-dioxanes adopt a twist-boat conformation with ca 25 ppm ^{13}C chemical shifts for the C(2) methyl groups. Small alkyl substituents such as nitriles and alkynes lead to significant population of the chair conformation, and the chair to twist-boat conformational equilibrium can be measured using the ^{13}C chemical shifts of the C(2) methyl groups.

The MM2 force field poorly predicts the conformational equilibrium between chair and twist-boat forms of 1,3-dioxanes. The MM3 force field and the PM3 semiempirical method lead to even worse predictions. The ordering of substituents is reasonably well modeled using either the semiempirical AM1 method or the ab initio 3-21G calculations, but the predicted reaction enthalpies are poor. Finally, the ab initio 6-31G* method with zero point energy corrections gives both reasonable ordering of substituents and reasonable predictions for conformational enthalpies. The experimental and calculated conformational energies described here should be useful in evaluating new molecular mechanics force fields.

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Supplementary Material Available: Characterization data for **4a–g** and **5a–g**, 6-31G* minima for the chair and twist-boat conformations of **6a–g**, and crystal structure diagram of **3** (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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