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Effect of Remote Aryl Substituents on the Conformational Equilibria of 2,2-Diaryl-1,3-dioxanes: Importance of Electrostatic Interactions

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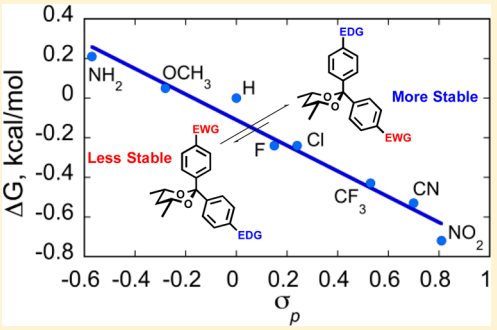
Supporting Information

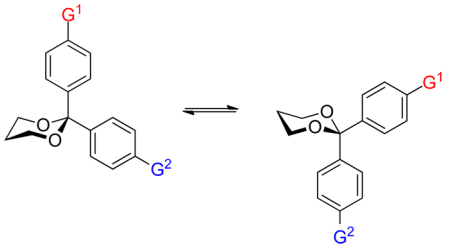
ABSTRACT: The conformational preference of a variety of 2,2-diaryl-1,3-dioxanes bearing remote substituents on the phenyl rings has been studied via equilibration of configurationally isomeric 2,2-diaryl-*cis*-4,6-dimethyl-1,3-dioxane epimers, X-ray crystallography, ^{1}H NOESY analysis, and B3LYP/6-311+G* calculations. When the aryl ring bears a remote electron-withdrawing substituent, the isomer having both the higher dipole moment and the electron-withdrawing group in the equatorial phenyl ring and/or an electron-donating group in the axial ring has the lower energy. These results differ from the conclusions reported in a previous study of similar systems. The conformational energy differences of *para*-substituted 2,2-diaryl-1,3-dioxanes are linearly related to the Hammett σ values with a slope (ρ) of 0.6. In addition, there is a trend toward longer bond lengths between the C(2) ketal center and the aryl ring as the electron-withdrawing nature of the *para*-substituent is increased. Electrostatic interactions, rather than a hyperconjugative anomeric effect, appear to be responsible for the conformational behavior of such molecules.



INTRODUCTION

Conformational issues lie at the heart of many chemical problems, but it is often difficult to determine the etiology of the conformational preference. This is certainly the case for the anomeric effect, a phenomenon that has been the subject of numerous studies and reviews.[1] One popular explanation for the effect, first suggested by Altona some 60 years ago,[2] is a hyperconjugative interaction involving electron delocalization of a lone pair into an adjacent C−X σ*-antibonding orbital. More recently, Mo[3] made use of valence bond theory to provide evidence that hyperconjugative interactions are not responsible for the anomeric effect and concluded that it is better interpreted as involving electrostatic interactions. In this connection, it is of some historical interest to note that electrostatic interactions were invoked by Lemieux and Chu, who coined the term "anomeric effect" in 1958, to account for the preference of axial over equatorial C-1 alkoxy groups in pyranose sugars.[4]

As a result of our interest in conformational preferences in substituted 1,3-dioxanes,[5,6] we made note of a 1999 report by Sato and co-workers dealing with the conformations of *para*-substituted 2,2-diphenyl-1,3-dioxanes.[7] These authors made the prescient suggestion that the geminal aryl rings have the same steric bulk and, consequently, the conformations preferentially adopted by such molecules, depicted below, should reflect the effect of the remote *para*-substituents on the conformational equilibria. Their NMR studies and X-ray crystallographic analyses of conformationally unbiased substrates led to the conclusion that the aryl group bearing the more electron-withdrawing *para*-substituent preferentially occupies the axial position and that the axial C(2)−aryl bond is significantly lengthened. They attributed this result to the operation of an anomeric effect involving a hyperconjugative interaction.



There was one disquieting observation in the account by Sato and co-workers:[7] they reported PM3 calculations that adequately reproduced the observed geometries but which indicated the opposite conformational preference for the *para*-substituted 2,2-diphenyl-1,3-dioxanes than that indicated by the crystallographic analyses; that is, the PM3 calculations suggested that the more electron-rich aryl group should preferentially adopt the axial position.

As we show below, the conclusions of Sato and co-workers, which were drawn from analysis of conformationally unbiased substrates whose crystal structures did not reflect the predominant conformation in solution, were incorrect. Remote substituents on the aryl rings do indeed have a considerable effect on the conformational equilibria of 2,2-diphenyl-1,3-

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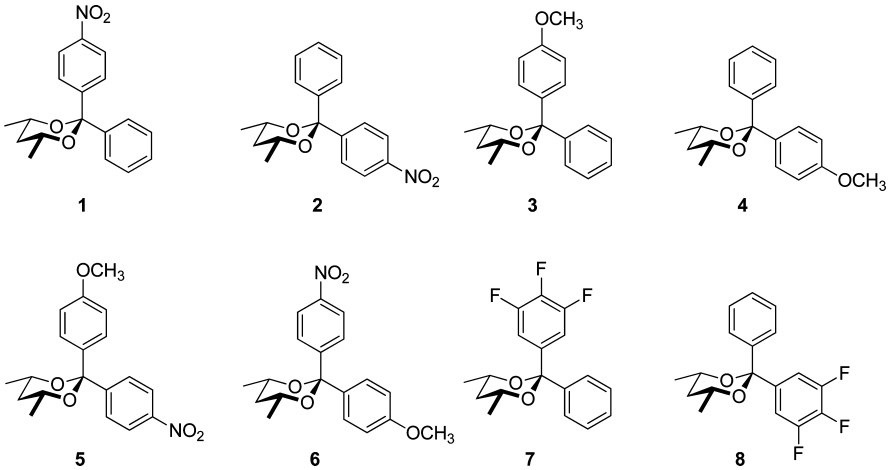
Chart 1. 2,2-Diaryl-*cis*-4,6-dimethyl-1,3-dioxanes

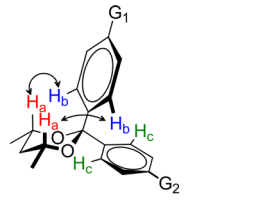


dioxanes. However, a hyperconjugative anomeric effect is likely not the correct explanation for the conformational behavior in these systems. As detailed below, analysis of the acid-catalyzed equilibria between configurationally isomeric 2,2-diphenyl-*cis*-4,6-dimethyl-1,3-dioxanes bearing remote aryl substituents demonstrate that electrostatic interactions are most likely responsible for the observed energy differences between isomers.

RESULTS AND DISCUSSION

Equilibration Studies. Seminal work by Eliel and co-workers has demonstrated that conformational equilibria of the sort depicted above are investigated most conveniently by acid-catalyzed equilibration of configurationally isomeric models for the conformational isomers, and a *cis*-4,6-dimethyl-1,3-dioxane is a good surrogate for the unbiased system.,[8] To this end, a representative series of anancomeric 2,2-diaryl-*cis*-4,6-dimethyl-1,3-dioxanes (**1**−**8**), depicted in Chart 1, were prepared by condensation of the appropriate benzophenone with *meso*-2,4-pentanediol. Fortunately, as suggested by the report by Nichols and co-workers,[9] it was not necessary to separate the *meso* diol from its racemic isomer: the ketone reacts preferentially with the *meso* diol to afford the desired *cis*-4,6-disubstituted dioxane rather than with the racemic diol to give the much less stable isomer bearing an axial methyl group. Thus, condensation of 2,4-pentanediol, consisting of ∼60% *meso* and ∼40% *dl* isomers,[10] with enough ketone to react with slightly less than the amount of *meso* diol present, provided as the major products the pairs of epimeric 1,3-dioxanes illustrated in Chart 1 along with a small quantity of the unwanted *trans*-4,6-dimethyl isomer. With some considerable effort, the 2,2-diaryl-*cis*-4,6-dimethyl-1,3-dioxanes epimers were separated chromatographically and recrystallized to give analytically pure solids.

The configuration of the individual 2,2-diaryl-*cis*-4,6-dimethyl-1,3-dioxanes were assigned by ^{1}H NOESY analysis of the interaction between the *ortho* protons of the axial aryl ring and the *syn*-axial protons at C(4,6) of the dioxane as illustrated below (and detailed in the Supporting Information).



A NOE is observed between H_a and H_b
A NOE is not observed between H_a and H_c

Additionally, the structures of compounds **1**−**4** were secured by X-ray crystallographic analysis; the structures, which are fully in accord with those assigned by NOESY analyses, are portrayed in Figure 1.

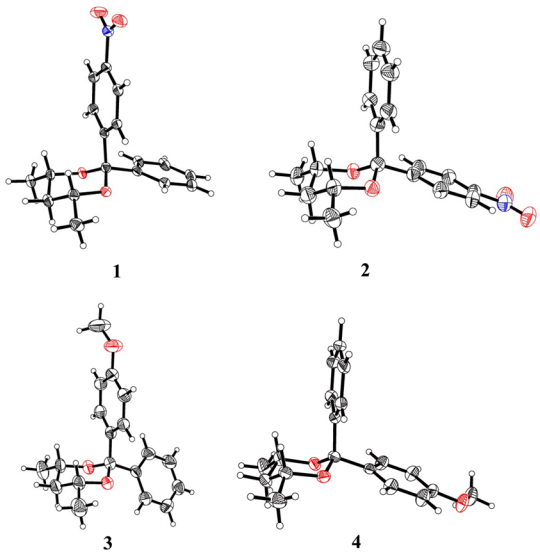


Figure 1. Crystal structures of compounds **1**−**4**. All thermal ellipsoids are shown at a 50% probability level, and hydrogen atoms are shown as arbitrary spheres.

Each of the 2,2-diaryl-*cis*-4,6-dimethyl-1,3-dioxane epimers were equilibrated at room temperature, as illustrated in Scheme 1, in sealed vials or ampules as solutions in cyclohexane, diethyl ether, and acetonitrile over Amberlyst-15 resin. Equilibrium was approached independently from pure samples of each isomer, and after the solutions were neutralized by shaking with anhydrous K_2CO_3, the area ratio of the isomers was determined by GC analysis that provided baseline separation. When the same area ratios were obtained from initially pure samples of each epimer, it was deemed that equilibrium had been attained. Area ratios for each equilibrium were taken as the average of 8−22 determinations from each side, and the free energy difference was calculated from this equilibrium constant as

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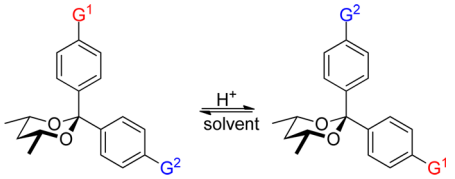
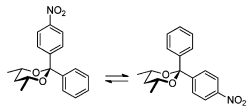
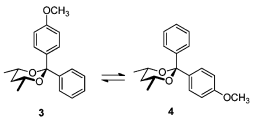
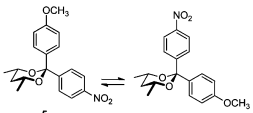
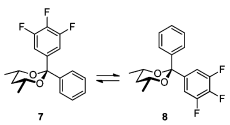
Scheme 1. Equilibration of 2,2-Diaryl-*cis*-4,6-dimethyl-1,3-dioxanes



$\Delta G^\circ = -RT \ln K$. The results of these studies are summarized in Table 1.

Table 1. Equilibria in 2,2-Diaryl-*cis*-4,6-dimethyl-1,3-dioxanes

entry	epimers	solvent	ΔG°,[a] kcal / mol
1		*c*-C_6H_{12}	not determined[b]
2		Et_2O	−1.31 ± 0.03
3		CH_3CN	−0.424 ± 0.001
4		*c*-C_6H_{12}	0.080 ± 0.003
5		Et_2O	0.038 ± 0.002
6		CH_3CN	−0.023 ± 0.002
7		*c*-C_6H_{12}	not determined[c]
8		Et_2O	0.78 ± 0.01
9		CH_3CN	0.199 ± 0.003
10		*c*-C_6H_{12}	−0.64 ± 0.01
11		Et_2O	−0.43 ± 0.01
12		CH_3CN	−0.101 ± 0.004

[a]Determined at 23 °C; errors are propagated standard deviations. [b]Equilibrium was not attained over the course of months. [c]Differences in the solubilities of **5** and **6** in cyclohexane precluded equilibration; **5** is quite soluble in cyclohexane, but **6** (the less stable isomer) precipitates from the equilibration solution.

Cursory inspection of the data presented in Table 1 demonstrates that the phenyl ring bearing the more electron-withdrawing substituent prefers to adopt the equatorial position at C(2) in 1,3-dioxane. These results are clearly contrary to the experimental observations reported by Sato and co-workers, but they are in accord with their semiempirical MO calculations.[7] It would appear that recrystallization of the conformationally mobile *para*-substituted 2,2-diphenyl-1,3-dioxanes used in the previous study led to the isolation of the less stable isomers. Before further discussion of the experimental results, it is instructive to consider the results of DFT calculations of the geometry and energetics of 2,2-diphenyl-*cis*-4,6-dimethyl-1,3-dioxanes bearing remote aryl substituents.

Computational Studies. In an effort to gain some insight into the factors responsible for the experimental results presented in Table 1, the 2,2-diaryl-*cis*-4,6-dimethyl-1,3-dioxanes were explored at the B3LYP/6-311+G* level[11] using tight convergence criteria (opt = verytight, int = ultrafine)[12] for both the optimizations and for calculation of the thermal corrections; all of the following data are for 298 K. The calculated enthalpies (ΔH°) and free energies (ΔG°) for the 1,3-dioxanes that were examined are summarized in Table 2. Using the tight optimization limits, the values of ΔH° and ΔG° are close to each other as might be expected for such similar compounds (e.g., $\Delta S^\circ \sim 0$). With compounds such as these, having many low frequencies, the correction from 0 K, as in the DFT calculations, to 298 K is more reliable for ΔH° than for ΔG°, and the former will be used in the following discussion when there is a significant difference between the values.

It can be noted that the computed geometries are in excellent agreement with the structures determined by X-ray crystallography. This aspect was investigated, as detailed in the Supporting Information, by mapping the crystallographic coordinates for compounds **1** and **2** onto the coordinates produced by computational optimization. The root-mean-square deviations (RMSDs) between atomic coordinates of all the non-hydrogen atoms of compounds **1** and **2** and the corresponding calculated atom positions had an average RMSD of 0.0852 Å for **1** and 0.0913 Å for **2**. Overall, the crystallographic and computational structures are remarkably similar.

The analogous conformationally mobile 2,2-diaryl-1,3-dioxanes lacking methyl groups were also examined at the same level of theory (details in the Supporting Information) and gave essentially the same results as those given in Table 2. Thus, as one might reasonably expect, the *cis*-4,6-dimethyl groups have a negligible effect on the conformational preference of the substituted phenyl rings.

It can be seen from the computational results presented in Table 2 that, in all cases, the isomer having the higher dipole moment, and having the electron-withdrawing group in the equatorial phenyl ring and/or the electron-donating group in the axial ring, is predicted to have the lower energy. That the higher dipole moment isomer is predicted to be more stable than its lower dipole moment epimer may seem surprising,[13] but this conclusion is fully consistent with the equilibration studies (Table 1). Indeed, the calculated ΔH° values in Table 2, which refer to the gas phase, are remarkably similar to the experimentally determined ΔG° values in cyclohexane (Table 1, entries 4 and 10), the least polar solvent used in the equilibration studies. The experimental free energy difference between **3** and **4** (ΔG° = 0.08 kcal/mol) as well as the value for **7** and **8** (ΔG° = 0.64 kcal/mol) match well with the computed ΔH° values of 0.07 and 0.54 kcal/mol, respectively, for these epimeric pairs (Table 2, entries 2 and 9). Unfortunately, as noted in Table 1, it was not possible to establish equilibrium in cyclohexane solution between the 1,3-dioxanes bearing NO_2-substituted phenyl rings.

The equilibration results demonstrate that the energy difference between each pair of epimeric *para*-substituted 2,2-diaryl-*cis*-4,6-dimethyl-1,3-dioxanes decreases as the polarity of the solvent increases. In the case of the *p*-methoxy pair (**3** and **4**), the preference for the isomer having the axial anisyl group, seen in cyclohexane and Et_2O solution, is reversed in CH_3CN. Given that the substituted 1,3-dioxanes are highly polar, one would expect that the difference in energy between epimeric pairs would vary in a polar medium where the electrostatic energies become small. However, it may seem surprising that the lower dipole moment isomer is apparently stabilized vis-à-vis the epimer of higher dipole moment as the solvent polarity

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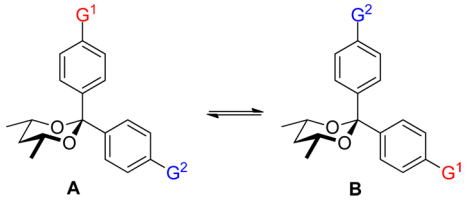
Table 2. Calculated Dipole Moments (μ), Enthalpies ($\Delta H°$), and Free Energies ($\Delta G°$) for *Para*-Substituted 2,2-Diphenyl-*cis*-4,6-dimethyl-1,3-dioxanes



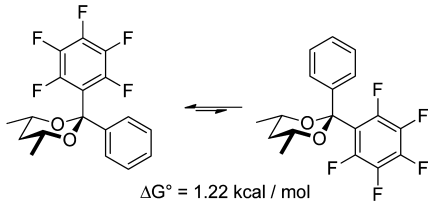
entry	G^1	G^2	A,[a] μ(D)	B,[a] μ(D)	$\Delta H°$,[b] A → B	$\Delta G°$,[b] A → B
1	NH_2	H	2.701	1.036	0.22	0.21
2	OMe	H	2.867	2.037	0.07	0.05
3	F	H	2.287	4.151	−0.26	−0.24
4	Cl	H	2.364	4.387	−0.24	−0.24
5	CF_3	H	3.334	5.949	−0.39	−0.43
6	CN	H	4.939	7.702	−0.55	−0.53
7	NO_2	H	5.255	8.037	−0.65	−0.65
8	NO_2	OMe	6.371	8.457	−1.07	−0.92
9	3,4,5-trifluoro	H	3.633	6.151	−0.54	−0.55

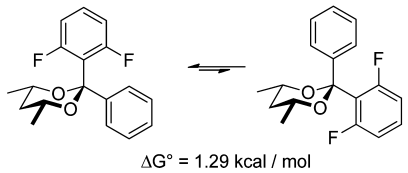
[a]Dipole moment. [b]kcal/mol; values are corrected for both differences in ZPE and the change in enthalpy on going from 0 K (corresponding to the calculations) to 298 K.

is increased. However, in most cases, the dipole is associated with a small group of atoms within a molecule; this is not true in the present case. The dipole moment of 1,3-dioxane is 2.23 D. Thus, the difference in dipole moments between epimers is largely due to an equatorial *para*-substituted aryl ring, having the substituent dipole oriented to enhance the ketal dipole, whereas it has less of an effect on the overall dipole moment when it is in the axial position.

In addition to the substituents listed in Table 2, the pentafluorophenyl epimers were examined. As illustrated in Scheme 2, the isomer having an axial pentafluorophenyl is

Scheme 2. Effect of *o*-Fluorophenyl Substituents





computed to be more stable ($\Delta G°$ = 1.22 kcal/mol) than its equatorial epimer. This axial preference, which contrasts to that of a *p*-fluorophenyl ($\Delta G°$ = −0.24 kcal/mol) or a 3,4,5-trifluorophenyl ring ($\Delta G°$ = −0.55 kcal/mol), is almost certainly related to a steric/electrostatic interaction involving the *o*-fluorine atoms and the oxygens of the 1,3-dioxane ring. Indeed, the 2,6-difluorophenyl group, lacking the more remote fluorines, prefers to adopt the axial orientation to an even greater extent ($\Delta G°$ = 1.29 kcal/mol) than its pentafluoro analogue.

Origin of the Substituent Effects. The observed substituent effects are remarkably well reproduced by the calculations. In large measure, this is likely due to the structural similarity between a given pair of epimers. The *para*-substituents are relatively far removed from the ketal center, and one would expect a large degree of cancellation of corresponding local atomic energies with the substituent providing only a small perturbation. The agreement between experimental and computed energy differences suggests that an analysis of the calculated results might lead to an explanation of the substituent effects.

The application of linear free energy relationships to probe substituent effects has a long history beginning with Hammett.[14] We have applied his use of σ_p constants[15] in the form of a plot giving the results shown in Figure 2. There is a very good linear correlation (r = 0.98), giving a slope (ρ) of −0.6, using either the calculated $\Delta H°$ or $\Delta G°$ values (Table 2). The sign of the slope (ρ value) suggests that the charge at the *ipso*-carbon of the phenyl ring attached to the C(2) ketal center becomes more positive as the substituent becomes more electron-withdrawing.

This conclusion is further reinforced by noting the effect of substituents on the bond length between the aryl rings and the C(2) ketal center; they are given in Table 3. In all cases, as would be expected on the basis of steric interactions,[16] the bond between C(2) and an axial phenyl ring is longer than the corresponding bond to an equatorial phenyl in both the parent molecule (Table 3, entry 5) and the *p*-substituted molecules. With the axial substituents, the C(2) to axial ring distances, by and large, increase as the *para* substituent is varied from those that are electron-donating to those that are electron-withdrawing. As noted above, the *ipso* carbon of the aryl ring becomes more positive as the aryl substituent becomes more electron-withdrawing. Given that the C(2) carbon is quite positive, this factor accounts for the increase in bond length.

It is possible to make the relationship between the atomic charges and the bond lengths more quantitative. This requires a calculation of the atomic charges from the wave function, and this can be done using the method developed by Hirshfeld[17] or the modification of this method that has been proposed more

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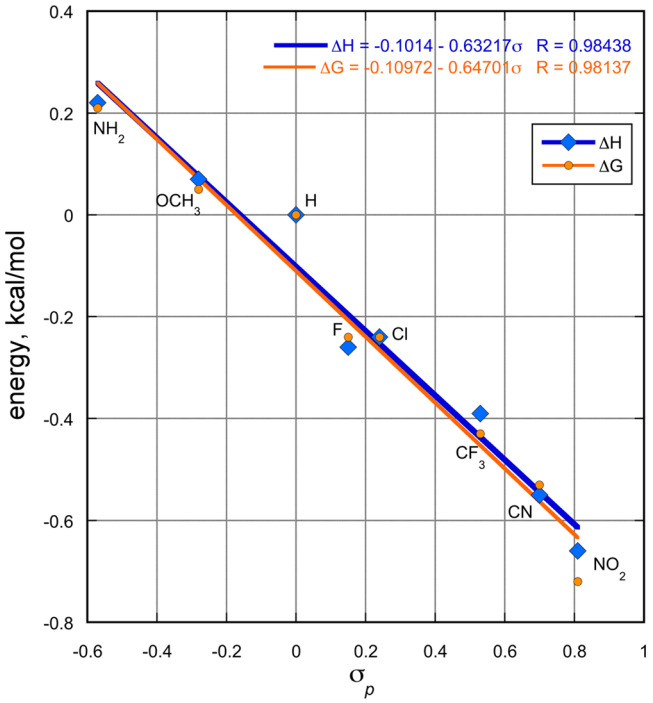
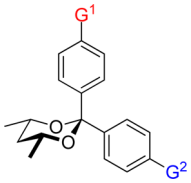


Figure 2. Hammett plot of calculated $\Delta H°$ and $\Delta G°$ values vs σ_p.

Table 3. C(2)−Aryl Bond Lengths in 2,2-Diaryl-*cis*-4,6-dimethyl-1,3-dioxanes



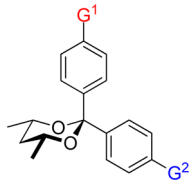
	substituted ring in axial position (G^1)		substituted ring in equatorial position (G^2)	
group	C(2)−axial length	C(2)−equatorial length	C(2)−axial length	C(2)−equatorial length
NH_2	1.5405	1.5302	1.5444	1.5248
OMe	1.5418	1.5302	1.5450	1.5272
H	1.5445	1.5305	1.5445	1.5305
F	1.5445	1.5303	1.5450	1.5292
Cl	1.5406	1.5302	1.5447	1.5294
CF_3	1.5460	1.5300	1.5445	1.5305
CN	1.5462	1.5302	1.5445	1.5305
NO_2	1.5460	1.5303	1.5446	1.5304

recently by Truhlar and co-workers.[18] We have calculated both of these charges and found them to be linearly related; the Hirshfeld charges are used in the following discussion.

The Hirshfeld charges at C(2) and at the *ipso*-position of the substituted aryl rings are listed in Table 4. The C(2) charge is largely unaffected by the *p*-substituents whereas the charge at the *ipso*-carbon varies from negative, for a ring bearing a *p*-NH_2, to a small positive value for a *p*-NO_2 group. The relationship between these charges (Table 4) and the C(2) to *ipso*-bond lengths of the axial phenyl rings bearing the substituent (Table 3) is shown in Figure 3. A similar trend is found for the epimers having the substituted ring in the equatorial position.

Could the difference in charges also be the origin of the substituent effects on the axial−equatorial energy differences? It

Table 4. Calculated Hirshfeld Charges at C(2) and the *Ipso*-Position of *Para*-Substituted Phenyl Rings in 2,2-Diaryl-*cis*-4,6-dimethyl-1,3-dioxanes



	G^1 = substituent G^2 = H		G^1 = H G^2 = substituent	
substituent	C(2)	*ipso*-carbon	C(2)	*ipso*-carbon
NH_2	0.1581	−0.0347	0.1579	−0.0161
OMe	0.1584	−0.0300	0.1583	−0.0164
H	0.1581	−0.0165	0.1581	−0.0165
F	0.1591	−0.0215	0.1586	−0.0127
Cl	0.1594	−0.0175	0.1583	−0.0164
CF_3	0.1596	−0.0067	0.1595	0.0033
CN	0.1594	−0.0029	0.1590	0.0067
NO_2	0.1596	0.0007	0.1591	0.0105

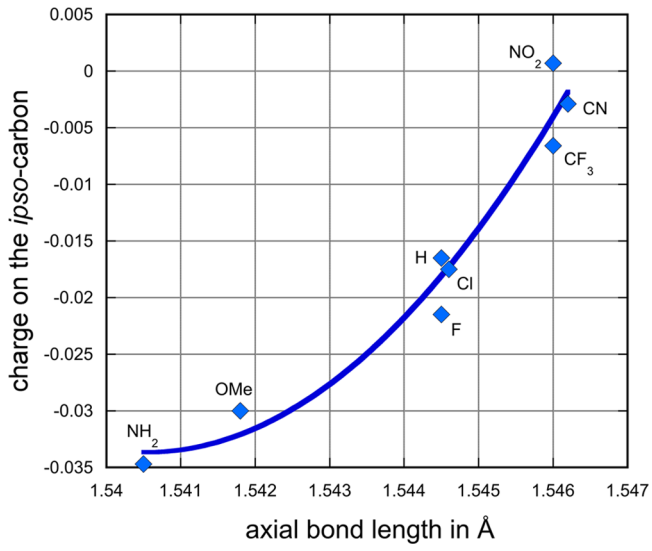


Figure 3. Relationship between the calculated Hirshfeld charges (Table 4) and the C(2)−*ipso*-bond lengths of the axial phenyl rings bearing the substituent.

would be tempting to sum all of the Coulombic energies between nonbonded atoms, but it is unlikely that this would be satisfactory. In the first place, the observed effects are quite small for these large molecules and, perhaps more importantly, there is no obvious way in which to implement this seemingly straightforward scheme. It was noted some time ago by Kirkwood and Westheimer that simple two-center calculated Coulombic energies in molecules are moderated by the electric fields associated with the bonds in a molecule.[19]

Thus, although the observed effects of remote aryl substituents on the conformational behavior of 2,2-diaryl-1,3-dioxanes are well reproduced by DFT calculations, the precise cause (or causes) of the observed effects remain somewhat obscure. It is clear, however, that electrostatic interactions, rather than a hyperconjugative anomeric effect, are responsible for the fascinating conformational behavior of such molecules.

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CONCLUSIONS

Remote substituents on the aryl rings of 2,2-diphenyl-1,3-dioxanes have a significant effect on the conformational equilibria of such molecules. Both the results of direct equilibration of configurationally isomeric 2,2-diphenyl-*cis*-4,6-dimethyl-1,3-dioxanes bearing remote aryl substituents (Table 1) and calculations at the B3LYP/6-311+G* level (Table 2) agree that, in all cases, the isomer having the higher dipole moment, and bearing an electron-withdrawing group in the equatorial phenyl ring and/or an electron-donating group in the axial ring, has the lower energy. These results are precisely the opposite of the conclusions reported by Sato and co-workers from their experimental observations drawn from a study of conformationally mobile 2,2-diaryl-1,3-dioxanes.[7]

The equilibration results indicate that the energy difference between each pair of epimeric *p*-substituted 2,2-diaryl-*cis*-4,6-dimethyl-1,3-dioxanes decrease as the polarity of the solvent increases.

The origin of the energy differences between epimeric pairs of 2,2-diphenyl −1,3-dioxanes bearing remote aryl substituents is likely electrostatic in nature. A Hammett plot, using either the calculated ΔH° or ΔG° values (Table 2) versus σ_p constants (Figure 2), is linear (r = 0.98) with a slope of −0.6. An analysis of computed atomic charges and bond length changes as the aryl substituents are varied is in accord with an explanation for the experimental results that invokes intramolecular electrostatic interactions as the dominant phenomenon. Unfortunately, as noted above, the specific etiology of the observed effects remain unclear.

EXPERIMENTAL SECTION

General Procedures. All commercially available reagents and solvents were of reagent grade and were used without further purification unless otherwise stated. Anhydrous solvents used for the equilibrium studies were dried as follows: dry diethyl ether and THF were freshly distilled from dark-purple solutions of sodium and benzophenone; cyclohexane was dried over anhydrous magnesium sulfate, filtered, and freshly distilled from a dark purple solution of sodium/benzophenone/tetraglyme; acetonitrile was distilled from calcium hydride. The method of Pritchard and Vollmer was followed for the preparation of 2,4-pentanediol as a mixture consisting of ∼60% *meso* and ∼40% racemic isomers.[10]

NMR spectra were recorded in $CDCl_3$ unless otherwise noted on a 400 MHz spectrometer, and chemical shifts are reported in ppm. Proton and carbon spectra are reported relative to TMS at δ = 0.00; fluorine spectra are reported relative to CCl_3F at δ = 0.00. Column chromatography was carried out on silica gel (40−63 μm particle size); one column volume of a solution of 0.5 mL of Et_3N in 250 mL of hexanes was run through the column before chromatography of the 2,2-diaryl-*cis*-4,6-dimethyl-1,3-dioxanes to prevent epimerization.

***r*-2-(*p*-Nitrophenyl)-*trans*-4,*trans*-6-dimethyl-2-phenyl-1,3-dioxane (1) and *r*-2-(*p*-Nitrophenyl)-*cis*-4,*cis*-6-dimethyl-2-phenyl-1,3-dioxane (2).** A mixture of 9.94 g (95.6 mmol) of 2,4-pentanediol, consisting of ∼60% *meso* and ∼40% racemic isomers, 10.00 g (44.0 mmol) of *p*-nitrobenzophenone, and 300 mg of Amberlyst-15 resin in 50 mL of cyclohexane was heated at reflux under a Dean−Stark trap for 5 d, at which point the theoretical amount of water had collected in the trap. The reaction mixture was allowed to cool to room temperature and was then filtered to remove the resin, 0.5 g of anhydrous Na_2CO_3 was added to the filtrate, and the mixture was stirred for 1 h to neutralize any residual acid. The mixture was then poured into a separatory funnel and washed four times with twice the volume of basic water (pH ≈ 10) to remove excess diol. The organic layer was dried (Na_2SO_4) and concentrated by rotary evaporation to yield 12.57 g (91%) of product as a mixture of three diastereomers. A 1.50 g portion of the product mixture was purified by flash chromatography on 60 g of silica gel using a 0−20% Et_2O/hexanes gradient. Three fractions were collected from the sample: 226 mg (15%) of **1** as white crystals, 582 mg (39%) of **2** as white crystals, and 285 mg (19%) of the unwanted isomer, *r*-2-(*p*-nitrophenyl)-*cis*-4,*trans*-6-dimethyl-2-phenyl-1,3-dioxane, as white crystals. The epimers, **1** and **2**, were distinguished using two-dimensional ^{1}H NOESY techniques as detailed in the Supporting Information. Each of the solid isomers were recrystallized, as described below, to give analytical samples used in the equilibration and crystallographic studies.

***r*-2-(*p*-Nitrophenyl)-*trans*-4,*trans*-6-dimethyl-2-phenyl-1,3-dioxane (1):** R_f = 0.23 (5% Et_2O/hexanes); mp 166−167 °C (30% Et_2O/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (d, J = 6.16 Hz, 6H), 1.44−1.54 (m, 2H), 3.88−3.96 (m, 2H), 7.21 (t, J = 7.24, 1H), 7.28 (t, J = 7.48, 2H), 7.54 (d, J = 7.60 Hz, 2H), 7.69, (d, J = 8.72 Hz, 2H), 8.22 (d, J = 8.72 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.9, 40.1, 67.8, 101.0, 124.4, 125.4, 128.3, 128.5, 128.5, 144.1,147.6, 149; HRMS (DART-TOF) m/z calcd for $C_{18}H_{19}NO_4$ $[M + H]^+$ 314.1392, found 314.1395.

***r*-2-(*p*-Nitrophenyl)-*cis*-4,*cis*-6-dimethyl-2-phenyl-1,3-dioxane (2):** R_f = 0.27 (5% Et_2O/hexanes); mp 142−143 °C (30% Et_2O/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (d, J = 6.16 Hz, 6H), 1.39−1.54 (m, 2H), 3.99−4.08 (m, 2H), 7.28 (t, J = 7.33, 1H), 7.39 (t, J = 7.49, 2H), 7.50 (d, J = 7.12 Hz, 2H), 7.75 (d, J = 9.00 Hz, 2H), 8.10 (d, J = 9.04 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.9, 40.2, 67.6, 100.9, 123.5, 126.6, 127.3, 128.4, 129.3, 140.3, 147.3, 152.0; HRMS (DART-TOF) m/z calcd for $C_{18}H_{19}NO_4$ $[M + H]^+$ 314.1392, found 314.1362.

***r*-2-(*p*-Nitrophenyl)-*cis*-4,*trans*-6-dimethyl-2-phenyl-1,3-dioxane:** R_f = 0.39 (5% Et_2O/hexanes); mp 108.5−110 °C (30% Et_2O/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (d, J = 2.24 Hz, 3H), 1.33 (d, J = 2.24 Hz, 3H), 1.71 (t, J = 7.68, 2H), 3.81−3.90 (m, 1H), 3.90−3.97 (m, 1H), 7.27 (t, J = 3.57, 1H), 7.33 (t, J = 7.38 Hz, 2H), 7.59 (d, J = 7.61 Hz), 7.78 (d, J = 8.88 Hz), 8.15 (d, J = 8.86 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 21.5, 41.2, 64.5, 64.7, 100.7, 123.5, 126.0, 127.0, 128.2, 128.4, 143.1, 147.4, 151.8; HRMS (DART-TOF) m/z calcd for $C_{18}H_{19}NO_4$ $[M + H]^+$ 314.1392, found 314.1396.

***r*-2-(*p*-Methoxyphenyl)-*trans*-4,*trans*-6-dimethyl-2-phenyl-1,3-dioxane (3) and *r*-2-(*p*-Methoxyphenyl)-*cis*-4,*cis*-6-dimethyl-2-phenyl-1,3-dioxane (4).** A mixture of 7.63 g (73.3 mmol) of 2,4-pentanediol, consisting of ∼60% *meso* and ∼40% racemic isomers, 7.18 g (38.8 mmol) of *p*-methoxybenzophenone and 200 mg (1.05 mmol) of *p*-TsOH in 50 mL of cyclohexane was heated at reflux under a Dean−Stark trap for 12 h, at which point the theoretical amount of water had collected in the trap. The reaction mixture was allowed to cool to room temperature, 0.5 g of anhydrous Na_2CO_3 was added to the filtrate, and the mixture was stirred for 1 h to neutralize any residual acid. The reaction was worked up as described above to yield 10.47 g (90.5%) of a clear, light yellow oil as a mixture of three diastereomers. A 1.50 g portion of the product mixture was purified by flash chromatography on 60 g of silica gel using a 0−15% Et_2O/hexanes gradient; the fractions were collected over anhydrous Na_2CO_3 to prevent epimerization of the isomers. Two fractions were collected from the sample: 118 mg (7.9%) of **3** as white crystals, and 285 mg (19%) of **4** as white crystals; the diastereomer resulting from condensation of the ketone with racemic 2,4-pentanediol was not collected, and was not further characterized, as it was not of interest. The epimers **3** and **4** were distinguished using two-dimensional ^{1}H NOESY techniques as detailed in the Supporting Information. Each of the solid isomers were recrystallized, as described below, to give analytical samples used in the equilibration and crystallographic studies.

***r*-2-(*p*-Methoxyphenyl)-*trans*-4,*trans*-6-dimethyl-2-phenyl-1,3-dioxane (3):** R_f = 0.41 (5% Et_2O/hexanes); mp 91.9−92.5 °C (pentane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (d, J = 6.16 Hz, 6H), 1.40−1.49 (m, 2H), 3.82 (s, 3H), 3.99−4.07 (m, 2H), 6.93 (d, J = 8.62 Hz, 2H), 7.19 (t, J = 7.28 Hz, 1H), 7.27 (t, J = 7.68 Hz, 2H), 7.44 (d, J = 8.68 Hz, 2H), 7.53 (d, J = 7.70 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.0, 40.4, 55.4, 67.1, 101.7, 114.3, 125.6, 127.7, 128.1, 128.9, 133.3, 145.8, 159.2; HRMS (DART-TOF) m/z calcd for $C_{19}H_{22}O_3$ $[M + H]^+$ 299.1647, found 299.1654.

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***r*-2-(*p*-Methoxyphenyl)-*cis*-4,*cis*-6-dimethyl-2-phenyl-1,3-dioxane (4):** R_f = 0.33 (5% Et_2O/hexanes); mp 101.2−102.5 °C (pentane); ^1H NMR (400 MHz, $CDCl_3$) δ 1.30 (d, J = 6.20 Hz, 6H), 1.36−1.46 (m, 2H), 3.73 (s, 3H), 3.94−4.02 (m, 2H), 6.78 (d, J = 8.80 Hz, 2H), 7.27 (t, J = 7.36 Hz, 1H), 7.38 (t, J = 7.80 Hz, 2H), 7.41 (d, J = 8.96 Hz, 2H), 7.50 (d, J = 7.80 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.0, 40.3, 55.4, 67.3, 101.8, 113.5, 127.1, 127.7, 127.7, 128.9, 138.2, 141.4, 159.2; HRMS (DART-TOF) m/z calcd for $C_{19}H_{22}O_3$ $[M + H]^+$ 299.1647, found 299.1654.

***r*-2-(*p*-Methoxyphenyl)-*trans*-4,*trans*-6-dimethyl-2-*p*-nitrophenyl-1,3-dioxane (5) and *r*-2-(*p*-Methoxyphenyl)-*cis*-4,*cis*-6-dimethyl-2-(*p*-nitrophenyl)-1,3-dioxane (6).** A mixture of 7.01 g (67.40 mmol) of 2,4-pentanediol, consisting of ∼60% *meso* and ∼40% racemic isomers, 7.98 g (31.05 mmol) of 4-methoxy-4′-nitrobenzophenone,[20] and 150 mg of Amberlyst-15 resin in 100 mL of cyclohexane was heated at reflux under a Dean−Stark trap for 3 d, at which point the theoretical amount of water had collected in the trap. The reaction mixture was worked up as described above to give 5.87 g (55%) of a clear, light yellow oil as a mixture of three diastereomers. A 400 mg portion of the product mixture was absorbed on 1 g of silica gel, and this sample was loaded on 65 g of silica. Column chromatography was performed by slowly increasing the volumetric ratio of ether to hexanes from 0% to 7% Et_2O/hexanes; 46 fractions (15−20 mL each) were collected once material began eluting from the column. Fractions 18−34 yielded 100 mg (25%) of **5** as a waxy, white solid. Fractions 38−46 yielded 99 mg (25%) of **6** as a waxy, white solid. The fractions containing the diastereomer resulting from condensation of the ketone with racemic 2,4-pentanediol were not further characterized. After concentration of the chromatographic fractions, pure samples of epimers **5** and **6** were obtained by fractional sublimation at 1 mm (**6** sublimes between 135−141 °C; **5** sublimes between 150−158 °C) followed by resublimation of each compound. The isomers were distinguished utilizing two-dimensional ^1H NOESY techniques as detailed in the Supporting Information. Each of the solid isomers were recrystallized, as described below, to give analytical samples used in the equilibration studies.

***r*-2(-*p*-Methoxyphenyl)-*trans*-4,*trans*-6-dimethyl-2-(*p*-nitrophenyl)-1,3-dioxane (5):** R_f = 0.24 (5% Et_2O/hexanes); mp 141.4−142.4 °C (resublimation), 137.8−139.1 °C (recrystallized from 3% Et_2O/hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 1.32 (d, J = 6.16 Hz, 6H), 1.41−1.53 (m, 2H), 3.80 (s, 3H), 4.00−4.08 (m, 2H), 6.91 (d, J = 8.80 Hz, 2H), 7.40 (d, J = 8.80 Hz, 2H), 7.73 (d, J = 9.00 Hz, 2H), 8.10 (d, J = 9.00 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.9, 40.3, 55.5, 67.4, 100.8, 114.7, 123.5, 126.5, 128.7, 132.2, 147.3, 152.3, 159.6; HRMS (DART-TOF) m/z calcd for $C_{19}H_{21}NO_5$ $[M + H]^+$ 344.1498, found 344.1498.

***r*-2-(*p*-Methoxyphenyl)-*cis*-4,*cis*-6-dimethyl-2-*p*-nitrophenyl-1,3-dioxane (6).** R_f = 0.15 (5% Et_2O/hexanes) mp 157.4−158.2 °C (resublimation); 156.1−157.1 °C (recrystallized from 3% Et_2O/hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 1.34 (d, J = 6.16 Hz, 6H), 1.42−1.53 (m, 2H), 3.73 (s, 3H), 3.84−3.93 (m, 2H), 6.80 (d, J = 8.96 Hz, 2H), 7.43 (d, J = 8.96 Hz, 2H), 7.67 (d, J = 8.86 Hz, 2H), 8.23 (d, J = 8.86 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.9, 40.0, 55.4, 67.8, 101.0, 113.7, 124.3, 126.8, 128.4, 136.7, 147.4, 149.5, 159.5; HRMS (DART-TOF) m/z calcd for $C_{19}H_{21}NO_5$ $[M + H]^+$ 344.1498, found 344.1501.

***r*-2-(3,4,5-Trifluorophenyl)-*trans*-4,*trans*-6-dimethyl-2-phenyl-1,3-dioxane (7) and *r*-2-(3,4,5-Trifluorophenyl)-*cis*-4, *cis*-6-dimethyl-2-phenyl-1,3-dioxane (8).** A mixture of 1.45 g (14.0 mmol) of 2,4-pentanediol, consisting of ∼60% *meso* and ∼40% racemic isomers, 3.00 g (12.7 mmol) of 3,4,5-trifluorobenzophenone, and 125 mg (0.656 mmol) of *p*-TsOH in 25 mL of cyclohexane was heated at reflux under a Dean−Stark trap for 9 d, at which point the theoretical amount of water had collected in the trap. Due to competitive dehydration of the diol during the course of the sluggish condensation, it was necessary to add an additional 14.0 mmol of 2,4-pentanediol on day 6. The reaction mixture was allowed to cool to room temperature, 0.5 g of anhydrous Na_2CO_3 was added to the filtrate, and the mixture was stirred for 1 h to neutralize any residual acid. The reaction was worked up as described above to yield 3.61 g (93%) of a white solid as a mixture of three diastereomers. Separation of compounds **7** and **8** was achieved by preparative TLC of a 50 mg portion of the mixture on a 1000 μm SiO_2 glass-backed plate using a 1% solution of Et_2O in hexanes as eluent: **7**, R_f = 0.47; **8**, R_f = 0.53. From this sample, 8 mg (16%) of **7** and 10 mg of **8** (20%) were isolated as a white solids. There was no attempt made to separate the diastereomer resulting from condensation of the ketone with racemic 2,4-pentanediol, as it was not of interest. The epimers **7** and **8** were distinguished using two-dimensional ^1H NOESY techniques as detailed in the Supporting Information. Each of the solid isomers were recrystallized, as described below, to give analytical samples used in the equilibration studies.

***r*-2-(3,4,5-Trifluorophenyl)-*trans*-4, *trans*-6-dimethyl-2-phenyl-1,3-dioxane (7):** mp 109.3−110.5 °C (pentane); ^1H NMR (400 MHz, $CDCl_3$) δ 1.32 (d, J = 6.10 Hz, 6H), 1.40−1.56 (m, 2H), 3.89−3.97 (m, 2H), 7.12 (dd, J = 6.8 Hz, J = 8.2, 2H), 7.22 (t, J = 7.2 Hz, 1H) 7.28 (t, J = 7.2, 2H), 7.44 (d, J = 7.3, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.9, 40.0, 67.7, 100.5, 111.6 (dd, J = 16.1 Hz, J = 6.0 Hz), 125.3, 128.3, 128.4, 138.5 (q, J = 5.5 Hz), 139.2 (dt, J = 250.0 Hz, J = 16.0 Hz), 144.3, 151.9 (ddd, J = 251.0 Hz, J = 10.3 Hz, J = 3.4 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −133.6 (dd, J = 20.4, 8.2 Hz), −161.8 (tt, J = 20.4, 6.8 Hz); HRMS (DART-TOF) m/z calcd for $C_{18}H_{17}F_3O_2$ $[M + H]^+$ 323.1259, found 323.1245.

***r*-2-(3,4,5-Trifluorophenyl)-*cis*-4, *cis*-6-dimethyl-2-phenyl-1,3-dioxane (8):** mp 99.1−99.8 °C (pentane); ^1H NMR (400 MHz, $CDCl_3$) δ 1.31 (d, J = 6.20 Hz, 6H), 1.36−1.51 (m, 2H), 3.94−4.02 (m, 2H), 7.17 (dd, J = 6.80 Hz, J = 8.8 Hz, 2H), 7.30 (t, J = 7.46 Hz, 1H) 7.40 (t, J = 7.40, 2H), 7.45 (d, J = 8.28, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.9, 40.1, 67.6, 100.4, 110.1 (dd, J = 16.1 Hz, J = 6.0 Hz), 127.3, 128.4, 129.3, 139.3 (dt, J = 250.0 Hz, J = 16.0 Hz), 140.1, 141.8 (q, J = 6.0 Hz), 150.9 (ddd, J = 248.6 Hz, J = 10.3 Hz, J = 3.4 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −135.2 (dd, J = 20.4, 8.8 Hz), −162.8 (tq, J = 20.4, 6.8 Hz); HRMS (DART-TOF) m/z calcd for $C_{18}H_{17}F_3O_2$ $[M + H]^+$ 323.1259, found 323.1287.

Equilibrations. For each pair of epimeric 2,2-diaryl-*cis*-4,6-dimethyl-1,3-dioxanes, equilibrium was approached independently from pure samples of each isomer. The epimers were equilibrated at room temperature (∼23 °C) in sealed vials or ampules as solutions in cyclohexane, Et_2O, and CH_3CN over Amberlyst-15 resin (20−30 beads). Periodically, samples were opened and neutralized by shaking with anhydrous K_2CO_3. The area ratio of the isomers was then determined by GC analysis using one of the following columns: a 30 m × 0.25 mm × 0.25 μm Optima-225 50% cyanopropyl/50% phenylmethyl polysiloxane column or a 30 m × 0.25 mm × 0.25 μm EC-1 100% dimethyl polysiloxane. The analysis parameters are detailed in the Supporting Information. When the same area ratios were obtained from initially pure samples of each epimer, it was deemed that equilibrium had been attained. Area ratios for each equilibrium were taken as the average of 8−22 determinations from each side. The equilibrium constant for a system was calculated from the area ratio of that system and the free-energy difference was evaluated as $\Delta G^\circ = -RT \ln K$ (Table 1). All reported errors (Table 1) are propagated standard deviations.[21]

X-ray Crystallography. All structures were solved by direct methods using SHELXS and refined against F^2 on all data by full-matrix least-squares with SHELXL.[22] All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included in the model at geometrically calculated positions and refined using a riding model. The isotropic displacement parameters of all hydrogen atoms were fixed to 1.2 times the U value of the atoms to which they are linked (1.5 times for methyl groups). The full numbering scheme of compounds **1**, **2**, **3**, and **4** can be found in the Supporting Information. Full details of the X-ray structure determination are located in the CIF, included in the Supporting Information. Additionally, CCDC nos. 1050759 (**1**), 1050760 (**2**), 1050761 (**3**), and 1050762 (**4**) contain the supplementary crystallographic data for this paper.[23]

Calculations. The calculations and the Hirshfeld charge calculations were carried out using Gaussian-09.[11]

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■ ASSOCIATED CONTENT

Supporting Information

NMR spectra of all products; ^{1}H NOESY spectra and analyses; details of the X-ray crystallography; analytical GC data; summary of the calculations, including computed energies and coordinates. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.

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