JOC The Journal of Organic Chemistry

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Controlling the Conformational Energy of a Phenyl Group by Tuning the Strength of a Nonclassical CH···O Hydrogen Bond: The Case of 5-Phenyl-1,3-dioxane

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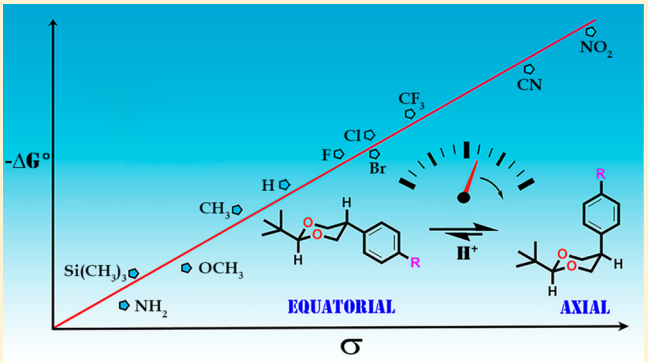
Supporting Information

ABSTRACT: Anancomeric 5-phenyl-1,3-dioxanes provide a unique opportunity to study factors that control conformation. Whereas one might expect an axial phenyl group at C(5) of 1,3-dioxane to adopt a conformation similar to that in axial phenylcyclohexane, a series of studies including X-ray crystallography, NOE measurements, and DFT calculations demonstrate that the phenyl prefers to lie over the dioxane ring in order to position an *ortho*-hydrogen to participate in a stabilizing, nonclassical CH···O hydrogen bond with a ring oxygen of the dioxane. Acid-catalyzed equilibration of a series of anancomeric 2-*tert*-butyl-5-aryl-1,3-dioxane isomers demonstrates that remote substituents on the phenyl ring affect the conformational energy of a 5-aryl-1,3-dioxane: electron-withdrawing substituents decrease the conformational energy of the aryl group, while electron-donating substituents increase the conformational energy of the group. This effect is correlated in a very linear way to Hammett substituent parameters. In short, the strength of the CH···O hydrogen bond may be tuned in a predictable way in response to the electron-withdrawing or electron-donating ability of substituents positioned remotely on the aryl ring. This effect may be profound: a 3,5-bis-CF_3 phenyl group at C(5) in 1,3-dioxane displays a pronounced preference for the axial orientation. The results are relevant to broader conformational issues involving heterocyclic systems bearing aryl substituents.

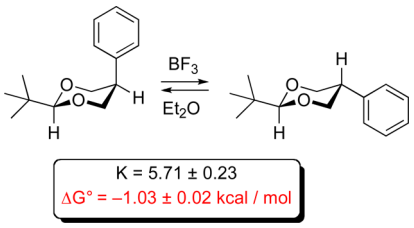


INTRODUCTION

Seminal, fundamental investigations by Eliel's group in the 1960s and 1970s of conformational equilibria in substituted 1,3-dioxanes have contributed significantly to the current understanding of the nature of steric and electronic effects in saturated heterocyclic systems.[1] The 1,3-dioxane system has three distinct sites of substitution, each of which displays a unique steric and stereoelectronic environment. Perhaps most importantly, facile acid-catalyzed equilibration of configurationally isomeric 1,3-dioxanes allows for accurate and precise determination of conformational energies.[2]

The conformational energy of a phenyl group at the C(5) position of 1,3-dioxane was determined in diethyl ether solvent at room temperature, as illustrated in Scheme 1, by Eliel and Knoeber in 1968 by BF_3-catalyzed equilibration of *cis*- and *trans*-2-*tert*-butyl-5-phenyl-1,3-dioxane.[3] Significantly, the energy difference, 1.03 ± 0.02 kcal/mol, is substantially lower than the 2.8 kcal/mol conformational energy (*A* value) of phenylcyclohexane.[4] The considerably lower conformational energy of 5-phenyl-1,3-dioxane vis-à-vis phenylcyclohexane was attributed at the time to "a diminution of the [syn-] axial interactions because, where in cyclohexane there are axial hydrogens in positions 1 and 3, in 1,3-dioxane there are, instead, electron pairs on oxygen".[5] In retrospect, given the results of more recent investigations of the conformational behavior of phenylcyclohexane, this explanation must be reassessed.

Scheme 1. Conformational Energy of 5-Phenyl-1,3-dioxane



The dominant interactions responsible for the sizable conformational energy of phenylcyclohexane, in which the plane of the axial phenyl ring is perpendicular to the benzylic C–H bond, are now known to be steric repulsion between the

Received: October 5, 2016
Published: November 16, 2016

DOI: 10.1021/acs.joc.6b02428
J. Org. Chem. 2016, 81, 12116–12127

equatorial hydrogens at the C(2) and C(6) positions of the cyclohexane ring and the ortho hydrogens of the axial phenyl group.[6] In short, syn-axial interactions contribute modestly, at best, to the conformational energy of phenylcyclohexane. Clearly, the same repulsive steric interactions present in phenylcyclohexane should beset an axial 5-phenyl group in the 1,3-dioxane system were it also to adopt a rotameric conformation having the plane of the ring perpendicular to the C(5) benzylic hydrogen. Given this background, the question remains: why is the conformational energy of a phenyl group in 5-phenyl-1,3-dioxane only a third as large as that of phenylcyclohexane?

An answer to the question is provided by an unanticipated result of our recent computational investigation of the rotameric conformations of a phenyl ring in a series of axially and equatorially substituted 1,3-dioxanes and tetrahydropyrans.[7] As shown below (Figure 1), the computed minimum

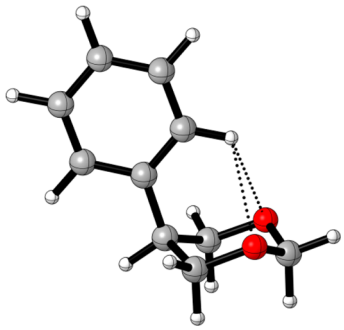


Figure 1. Calculated minimum energy rotamer of axial 5-phenyl-1,3-dioxane.

energy rotamer of axial 5-phenyl-1,3-dioxane is one in which the plane of the phenyl ring bisects the 1,3-dioxane ring and is parallel to the benzylic C(5)−H bond. This arrangement positions an ortho hydrogen proximate to the two ring oxygens, leading to attractive CH···O Coulombic interactions.

To the extent that the computational results comport with reality, we reasoned that the strength of the nonclassical CH···O hydrogen bond[8] between an ortho hydrogen and a ring oxygen in axial 5-phenyl-1,3-dioxane should respond to substituents placed remotely on the phenyl ring: electron-withdrawing groups should strengthen the attractive CH···O interaction, and electron-donating groups should attenuate the interaction. As demonstrated by the results presented below, this is indeed the case.

RESULTS AND DISCUSSION

Equilibration Studies. At the outset of the study, *cis*- (**1**) and *trans*-2-isopropyl-5-phenyl-1,3-dioxane (**2**) were prepared in order to demonstrate, once again,[3] that the nature of the 2-alkyl holding group has no effect on the conformational energy of a C(5) substituent determined by direct equilibration of the 1,3-dioxane isomers. A representative series of anancomeric 2-*tert*-butyl-5-aryl-1,3-dioxanes (**3**−**14**), depicted in Chart 1, were also prepared as illustrated in Scheme 2 by acid-catalyzed condensation of pivaldehyde with 2-aryl-1,3-propanediols. The diastereoisomeric pairs of 5-aryl-1,3-dioxanes were, with some difficulty, separated chromatographically and fully characterized. The configuration of the individual dioxane isomers follows from the method of preparation of each pair: in every case but one (discussed below), the thermodynamically more stable trans isomer (even numbered compounds in Chart 1) was the major product of the condensation reactions. Nonetheless, the configurations were further confirmed by ^{1}H NOESY analysis as detailed in the Supporting Information.

An X-ray crystallographic analysis of *cis*-2-*tert*-butyl-5-(*p*-chlorophenyl)-1,3-dioxane (**3**), portrayed in Figure 2, corroborates the computational result noted in above. There are two chemically identical, but crystallographically distinct molecules in the asymmetric unit. The axial phenyl ring in both cases adopts a rotameric arrangement in which an otho hydrogen is in close proximity to one of the dioxane oxygen atoms. The CH···O distances in each of the molecules in the unit cell (Table 7, Supporting Information) are virtually identical: 2.41(2) and 2.44(2) Å.

Each of the 5-aryl-1,3-dioxane pairs (**1**−**14**) were equilibrated at room temperature (~23 °C) in sealed ampules under nitrogen as solutions in either cyclohexane or diethyl ether over dry Amberlyst-15 resin. Equilibrium was approached independently from samples of the cis isomer and the trans isomer, and after the solutions were neutralized by shaking with anhydrous K_2CO_3, the area ratio of the isomeric mixture was determined by capillary GC analysis to provide baseline separation. It was deemed that equilibrium had been reached when the same area ratios were obtained from initially pure samples of each isomer. Area ratios for each equilibration, which reflect the equilibrium constant for the process, were taken as the average of 5−14 independent determinations from each side, and the free energy difference for the equilibrium was calculated in the normal way: $\Delta G^\circ = -RT \ln K$. The results of these studies are summarized in Table 1.

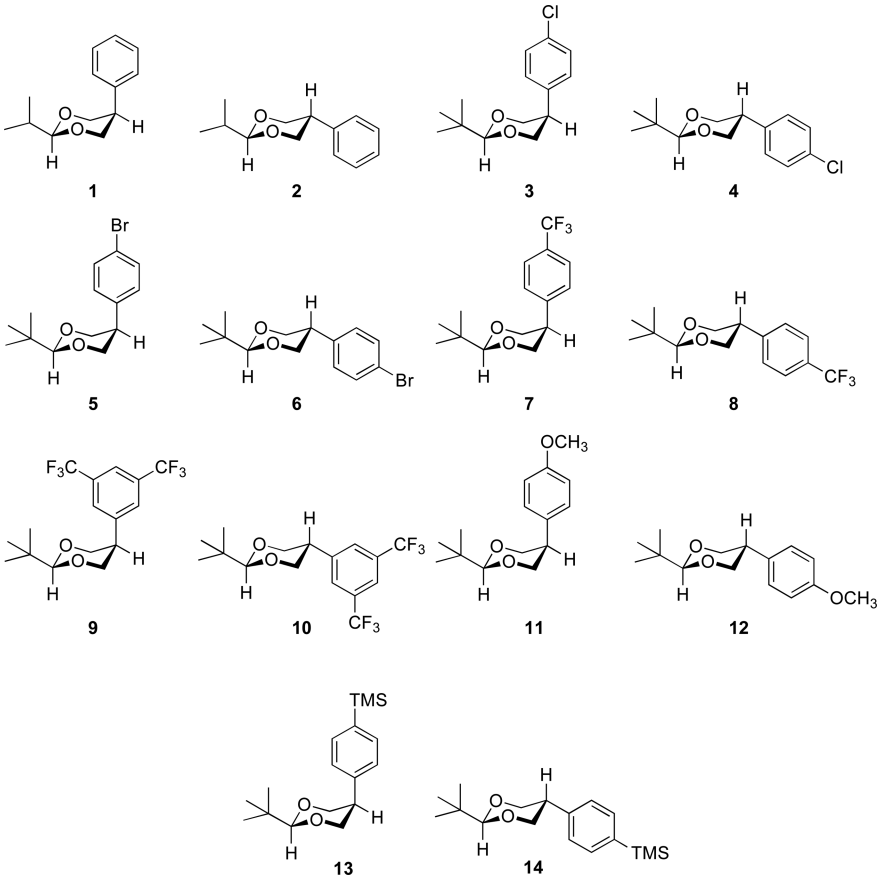
As expected, the conformational energy of 5-phenyl-1,3-dioxane in diethyl ether solvent determined by equilibration of compounds **1** and **2** having a 2-isopropyl holding group (−1.06 kcal/mol; Table 1, entry 2) is identical, within combined experimental error, to that reported by Eliel and Knoeber from equilibration of 2-*tert*-butyl-5-phenyl-1,3-dioxane (−1.03 kcal/mol).[3] The effect of solvent on the conformational energies of the 5-aryl groups is, on the whole, rather minimal: for a given pair of isomers, the difference in ΔG° is on the order of 0.01−0.17 kcal/mol. The more significant conclusion to be drawn from the results is that substituents on the phenyl ring, as remote as the para position, affect the conformational energy of a phenyl group.

Cursory inspection of the data presented in Table 1 demonstrates that electron-withdrawing substituents (*p*-Cl, *p*-Br, *p*-CF_3, and 3,5-bis-CF_3) stabilize the cis isomer, while electron-donating groups (*p*-OMe and *p*-TMS) have a destabilizing effect. Remarkably and unexpectedly, a 3,5-bis-CF_3 phenyl group actually displays a pronounced preference for the axial orientation in both cyclohexane and acetonitrile (Table 1, entries 9 and 10). To our knowledge, this is an unprecedented result.

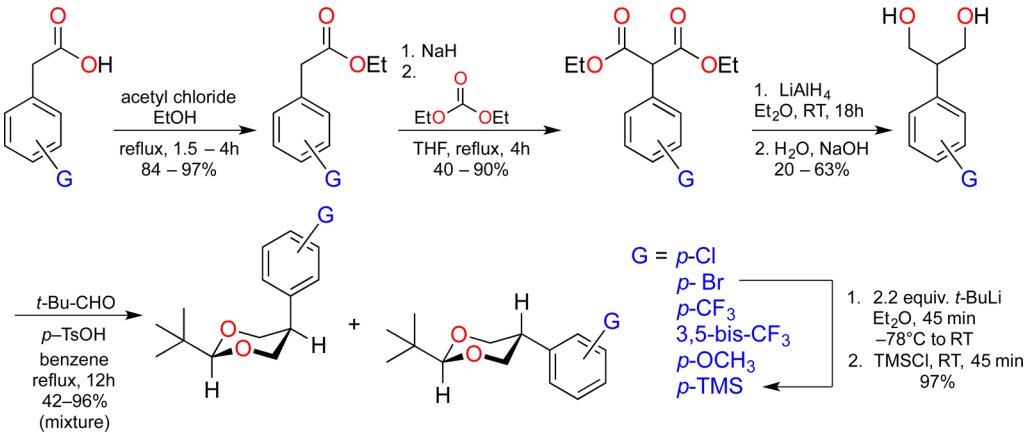
The etiology of the effect of substituents on the strength of the CH···O hydrogen bond and, hence, the conformational energy of a 5-phenyl-1,3-dioxane, is very likely electrostatic. A Hammett plot of the experimental ΔG° values in cyclohexane solution from Table 1 versus σ_m constants,[9] derived from the pK_a's of substituted benzoic acids, is shown in Figure 3. There is a good linear correlation (r = 0.98) having a slope (ρ) of +1.5. In this connection, it might be noted that para substituents are meta with respect to the ortho hydrogen of the phenyl ring that interacts with a ring oxygen. The linear correlation strongly suggests that the effect of substituents on

DOI: 10.1021/acs.joc.6b02428
J. Org. Chem. 2016, 81, 12116−12127

Chart 1. Anancomeric 5-Aryl-1,3-dioxanes



Scheme 2. Preparation of 2-*tert*-Butyl-5-aryl-1,3-dioxanes



the conformational energy of a 5-phenyl-1,3-dioxane has the same origin as the effect of those substituents on the acidity of benzoic acid: an inductive, electrostatic phenomenon. The picture that emerges is one in which electron-withdrawing substituents render the ortho hydrogens of the axial C(5) phenyl group more positive, thus increasing the attractive CH···O hydrogen bond of that hydrogen with an oxygen of the 1,3-dioxane.

This conclusion is further reinforced by the behavior of *cis*-2-*tert*-butyl-5-(2-pyridyl)-1,3-dioxane (**15**) and *trans*-2-*tert*-butyl-5-(2-pyridyl)-1,3-dioxane (**16**) as well as that of their corresponding pyridinium bromide salts, **17** and **18**. As illustrated in Scheme 3, acid-catalyzed condensation of 2-(2-pyridyl)-1,3-propanediol with pivaldehyde gave a mixture of the salts of **15** and **16** containing a preponderance of the salt of the cis isomer (**15**). Neutralization of the reaction mixture and separation of the free amines afforded pure, crystalline *cis*-2-*tert*-butyl-5-(2-pyridyl)-1,3-dioxane (**15**): the X-ray structure of this material is shown in Figure 4. The molecule adopts a rotameric conformation in which the pyridyl ring very nearly eclipses the C(4)−C(5) bond of the dioxane. The torsion angle made by the pyridyl ring and C(4)−C(5) bond is 7.51(12)° and positions the nitrogen atom away from the ring oxygens.

Each of the free amines was converted to a pyridinium bromide in high yield under neutral conditions by reaction with *t*-BuBr in chloroform solution (Scheme 3).[10] The cis salt (**17**)

DOI: 10.1021/acs.joc.6b02428
J. Org. Chem. 2016, 81, 12116−12127

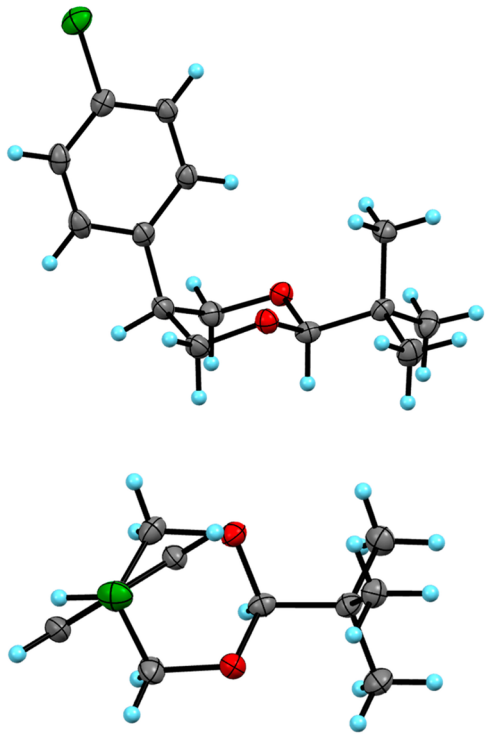


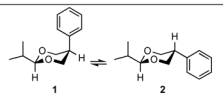
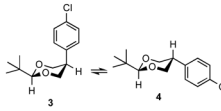
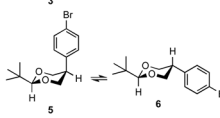
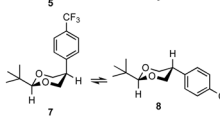
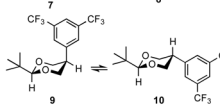
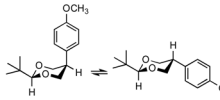
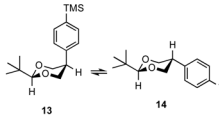
Figure 2. Crystal structure of *cis*-2-*tert*-butyl-5-(*p*-chlorophenyl)-1,3-dioxane (**3**). All thermal ellipsoids are shown at a 50% probability level, and hydrogen atoms are shown as arbitrary spheres. The top view is from the side; the lower view, from above, shows the CH···O interaction.

is quite stable both as a solid and in chloroform solution; the trans diastereoisomer, **18**, rapidly isomerizes to **17**, particularly in solution. Apparently, the acidic hydrobromide catalyzes equilibration of **17** to **18**. At what we assume to be equilibrium, there is less **18** present than can be detected by ^{1}H NMR, and we estimate that the ΔG° (**17** ⇌ **18**) exceeds 4.0 kcal/mol. Clearly, the classical hydrogen bond that presumably stabilizes the axial salt (**17**) is an extreme manifestation of the equivalent electrostatic CH···O interaction responsible for the effect of remote substituents on the conformational energy of 5-phenyl-1,3-dioxanes.

Before consideration of the results of DFT calculations, described below, that support this conclusion, it is important to note that the entropy contribution to the ΔG° in these systems is negligible. The results of a study of the effect of temperature on the acid-catalyzed equilibrium of between *cis*-2-isopropyl-1,3-dioxane (**1**) and its trans isomer (**2**) in cyclohexane solution are summarized in Table 2. A van't Hoff plot, ln K vs T^{-1}, of the equilibrium data, having a correlation coefficient of r = 0.99, is shown in Figure 5. The slope of the plot is $\Delta H^\circ/R$, where ΔH° is the conformational enthalpy difference between the isomers and the intercept is $\Delta S^\circ/R$, where ΔS° is the conformational entropy difference. The slope of the plot leads to $\Delta H^\circ = -1.06 \pm 0.06$ kcal/mol, and the intercept gives $\Delta S^\circ = +0.03 \pm 0.09$ eu. The results demonstrate that the entropy contribution to ΔG° is insignificant.

Computational Studies. In an effort to achieve further insight into the origin of the effect of aryl substituents on the conformational energy of 5-aryl-1,3-dioxanes (Table 1), the 2-*tert*-butyl-5-aryl-1,3-dioxanes were explored using density functional theory calculations at the B3LYP/6-311+G* level[11] using tight convergence criteria (opt = very tight, int = ultrafine) for both the optimizations and for calculation of thermal corrections; all of the following data are for 298 K. Details of the calculations may be found in the Supporting

Table 1. Equilibria in 5-Phenyl-1,3-dioxanes[a]

entry	dioxanes	solvent	K	ΔG°, kcal/mol
1		C_6H_{12}	5.71 ± 0.05	−1.03 ± 0.01
2		Et_2O	6.09 ± 0.07	−1.06 ± 0.01
3		C_6H_{12}	3.19 ± 0.07	−0.68 ± 0.01
4		Et_2O	3.25 ± 0.07	−0.69 ± 0.01
5		C_6H_{12}	3.06 ± 0.01	−0.66 ± 0.01
6		Et_2O	3.19 ± 0.01	−0.68 ± 0.01
7		C_6H_{12}	2.31 ± 0.02	−0.49 ± 0.01
8		Et_2O	3.10 ± 0.01	−0.67 ± 0.01
9		C_6H_{12}	0.63 ± 0.01	+0.27 ± 0.01
10		CH_3CN[b]	0.68 ± 0.01	+0.22 ± 0.01
11		C_6H_{12}	6.35 ± 0.02	−1.09 ± 0.01
12		Et_2O	5.73 ± 0.04	−1.03 ± 0.01
13		C_6H_{12}	7.17 ± 0.12	−1.16 ± 0.02
14		Et_2O	6.70 ± 0.14	−1.12 ± 0.01

[a]Determined at room temperature: errors in K are propagated standard deviations; the errors in ΔG° are estimated errors that are larger than the propagated standard deviation to account for an assumed GC response ratio of 1.0 for a given pair of isomers. [b]During the slow equilibration of **9** and **10** in Et_2O, partial decomposition of the dioxanes to unidentified products was observed, and for this reason, the data for this experiment are not reported.

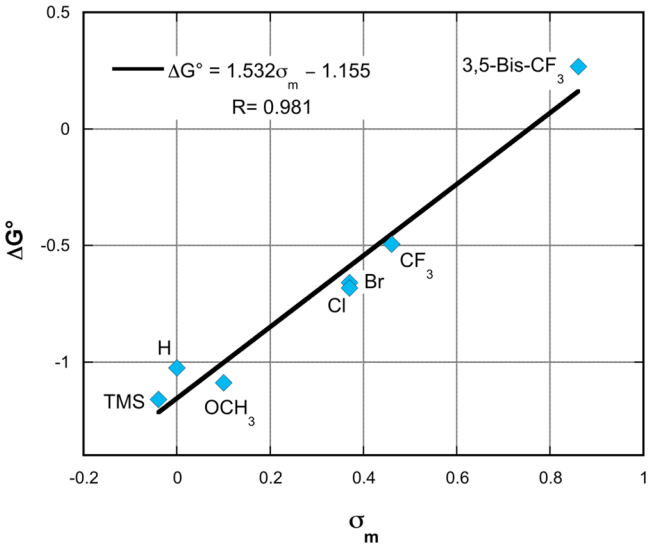
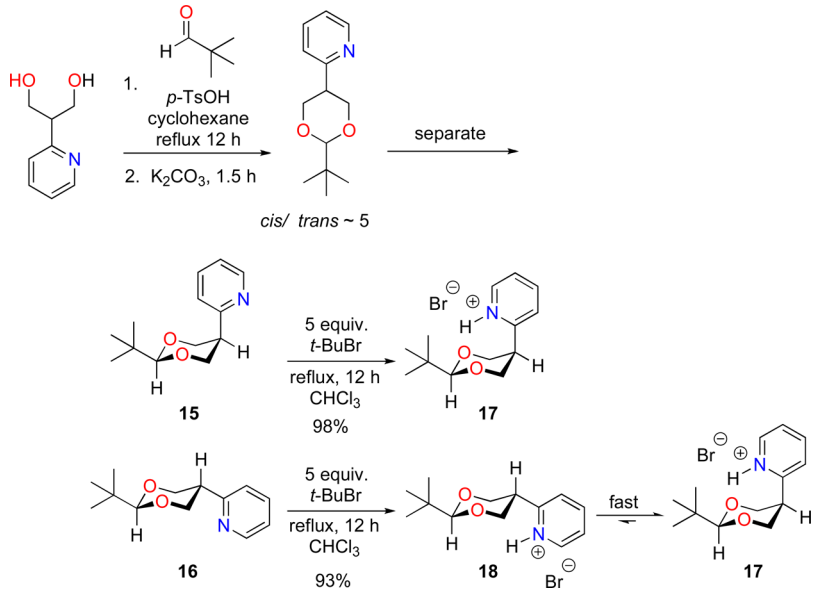


Figure 3. Hammett plot of experimental ΔG° values (Table 1) determined in cyclohexane solution vs σ_m values. The σ for the 3,5-di-CF_3 case was calculated from the pK_a of 3,5-bis-CF_3 benzoic acid.

DOI: 10.1021/acs.joc.6b02428
J. Org. Chem. 2016, 81, 12116−12127

Scheme 3. Preparation of 2-*tert*-Butyl-5-(2-pyridyl)-1,3-dioxanes (15 and 16) and Their HBr Salts (17 and 18)



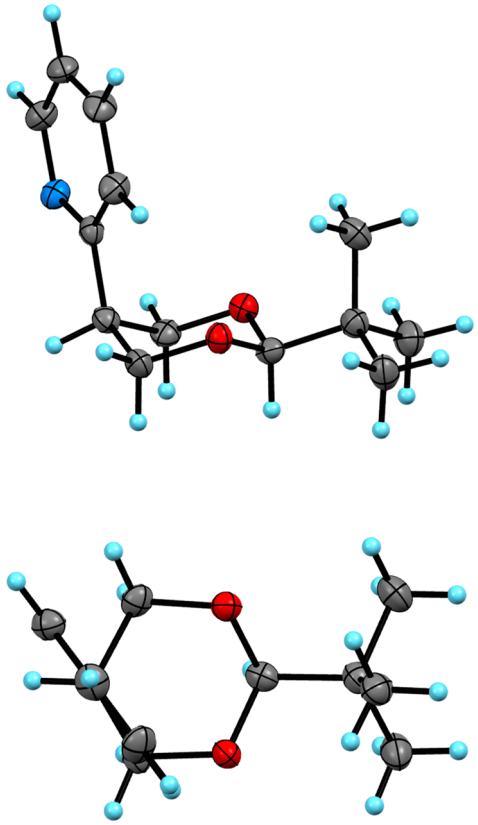


Figure 4. Crystal structure of *cis*-2-*tert*-butyl-5-(2-pyridyl)-1,3-dioxane (**15**). All thermal ellipsoids are shown at a 50% probability level, and hydrogen atoms are shown as arbitrary spheres. The top view is from the side; the lower view is from above.

Table 2. Effect of Temperature on the Acid-Catalyzed Equilibrium of *cis*- (1) and *trans*-2-Isopropyl-5-phenyl-1,3-dioxane (2) in Cyclohexane Solution

entry	temp (°C)	*K*	ΔG° (kcal/mol)
1	39.8	5.58 ± 0.04	−1.07 ± 0.01
2	56.1	5.14 ± 0.04	−1.07 ± 0.01
3	66.0	4.81 ± 0.04	−1.06 ± 0.01
4	77.1	4.69 ± 0.04	−1.08 ± 0.01

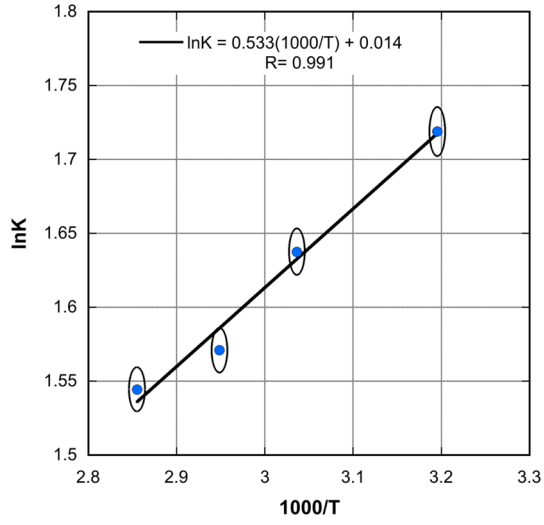


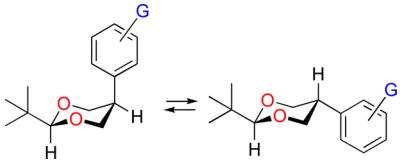
Figure 5. van't Hoff plot of the equilibrium data summarized in Table 2.

Information. The 2-*tert*-butyl-5-aryl-1,3-dioxanes have many relatively uncertain low frequencies and the correction from 0 K, as in the DFT calculations, to 298 K is more reliable for ΔH° than for ΔG°; the former is used in the following discussion. In any event, as demonstrated above, the entropy contribution to ΔG° is essentially zero.

Table 3 summarizes the computed substituent effects on the conformational enthalpies ($\Delta\Delta H^\circ$), corrected for differences in zero-point energies and thermal corrections to 25 °C, with the experimental substituent effects ($\Delta\Delta G^\circ$ from Table 1). Overall, there is a good correspondence between the experimental and calculated values. Since we are interested primarily on the effect aryl substituents may have on the strength of the interaction between the proximate *ortho*-hydrogen of an axial phenyl ring with an oxygen of the 1,3-dioxane, it was of interest to explore

DOI: 10.1021/acs.joc.6b02428
J. Org. Chem. 2016, 81, 12116−12127

Table 3. Comparison of Experimental and Calculated Substituent Effects on the Conformational Equilibria of 2-*tert*-Butyl-5-aryl-1,3-dioxanes



G	$\Delta\Delta G°$ from Table 1[a] relative to G = H	calcd $\Delta\Delta H°$ relative to G = H	q(H)[b] (e)	q(O)[c] (e)
H	0.00	0.00	0.0432	−0.1800
p-Cl	0.35	0.36	0.0472	−0.1760
p-Br	0.37	0.43	0.0476	−0.1636
p-CF_3	0.54	0.65	0.0471	−0.1633
3,5-bis-CF_3	1.30	1.26	0.0509	−0.1648
p-OMe	−0.06	−0.09	0.0452	−0.1639
p-TMS	0.13	0.06	0.0428	−0.1636

[a]In cyclohexane solution. [b]Hirshfeld charge on the *ortho*-hydrogen proximate to the ring oxygen. [c]Hirshfeld charge of the ring oxygen closest to the *ortho*-hydrogen.

the charges on the atoms involved in this electrostatic interaction. The calculation of charge distribution within a molecule is fraught with difficulty; such quantities are not well-defined. We have chosen to use Hirshfeld charges derived from the electron density distributions.[12] The effect of substituents on the charges at both the *ortho*-hydrogen of the phenyl ring and the dioxane oxygen with which it interacts are summarized in Table 3. Not surprisingly, the positive charge on the *ortho*-hydrogen increases as the substituent becomes more electron-withdrawing and decreases in the case of an electron-donating TMS substituent. Qualitatively, the Coulombic energy associated with these intramolecular electrostatic CH···O interactions accounts nicely for the effect of remote aryl substituents on the conformational energy of 5-phenyl-1,3-dioxane. Beyond that, as we have noted previously,[13] it would not be prudent to attempt to quantitate the effect by summation of Coulombic energies ($E = q_1q_2/r_{12}$) between the nonbonded atoms because, as demonstrated by Kirkwood and Westheimer, simple two-center calculated Coulombic energies in molecules are attenuated by electric fields associated with the bonds in a molecule.[14]

CONCLUSIONS

In agreement with the results of a recent computational study,[7] the minimum energy rotameric conformation of an axial 5-phenyl-1,3-dioxane has been demonstrated to be one that positions the aryl ring such that an *ortho*-hydrogen is in close proximity to one of the dioxane ring oxygens (Figure 1). The results described above demonstrate that the strength of this nonclassical CH···O hydrogen bond may be tuned in response to the electron-withdrawing or electron-donating ability of substituents positioned remotely on the aryl ring.

Acid-catalyzed equilibration of a representative series of anancomeric 2-*tert*-butyl-5-aryl-1,3-dioxane isomers (Table 1) reveals that substituents on the phenyl ring affect the conformational energy of a 5-phenyl-1,3-dioxane in a predictable and quite reasonable way: electron-withdrawing substituents decrease the conformational energy of the phenyl group, while electron-donating substituents increase the conformational energy of the group. Moreover, the effect of substituents on the conformational energy of a 5-phenyl-1,3-dioxane is correlated in a very linear fashion (r = 0.98) to Hammett σ_m parameters (Figure 3). Consequently, the conformational energy of a 5-phenyl group is adjustable, or tunable, in a predictable and rather precise way by reference to Hammett constants that account for the effect of substituents on the acidity of benzoic acids.

In a larger sense, the results of this investigation of the conformational behavior of 5-phenyl-1,3-dioxanes reinforce the notion that nonclassical CH···X hydrogen bonds are often relevant to an understanding of broader conformational issues involving heterocyclic systems bearing aryl substituents.

EXPERIMENTAL SECTION

General Procedures. Anhydrous solvents were obtained as follows: dry Et_2O and THF were freshly distilled from a dark-purple solution of sodium and benzophenone; cyclohexane was dried over anhydrous magnesium sulfate, filtered, and freshly distilled from a dark blue solution of sodium/benzophenone/tetraglyme; acetonitrile was distilled from calcium hydride; dry $CHCl_3$ was obtained by stirring with anhydrous potassium carbonate then passage through a short column of activated alumina. Reactions involving organometallic reagents were conducted in flame-dried glassware under an argon atmosphere using standard techniques for handling air-sensitive reagents,[15] solvents were deoxygenated by bubbling dry argon gas through the neat liquid for 10 min before use, and *tert*-butyllithium was titrated immediately prior to use utilizing the method of Watson and Eastham.[16] Sodium hydride, purchased as a 60% dispersion in mineral oil, was washed with pentane to remove the mineral oil coating prior to use. NMR spectra were recorded in $CDCl_3$ on a 400 or 500 MHz spectrometer, and chemical shifts are reported in ppm. Proton spectra are referenced to the residual ^{1}H signal of $CHCl_3$ at δ = 7.26 and are reported relative to TMS at δ = 0.00; carbon spectra are referenced to the ^{13}C signal for $CDCl_3$ at δ = 77.23 and are reported relative to TMS at δ = 0.00; fluorine spectra are referenced to a fluorobenzene internal standard at δ= −113.15 and are reported relative to CCl_3F at δ = 0.00. Residual acid present in the $CDCl_3$ NMR solvent was neutralized with the addition of and storage over anhydrous potassium carbonate to prevent epimerization of products. HRMS molecular mass determinations were performed on a TOF mass spectrometer using a direct analysis in real time (DART) ionization method. Refractive indices and melting points are uncorrected.

Synthesis of Ethyl Esters. *Ethyl 2-(4-Chlorophenyl)acetate.*[17] Following the general method of Xu and co-workers,[18] 100 mL of absolute ethanol was added to a 250 mL round-bottomed flask containing a magnetic stir bar followed by the addition of 21.32 g (125.0 mmol) of 4-chlorophenylacetic acid and 9.80 mL (138 mmol) of acetyl chloride. The flask was fitted with a condenser and heated in an oil bath to 50 °C for 1.5 h and then allowed to cool to room temperature. Solvent was removed under reduced pressure, and the residue was taken up in 100 mL of Et_2O and washed with saturated aqueous $NaHCO_3$ (3 × 50 mL), brine (1 × 25 mL), dried over Na_2SO_4, and concentrated to afford 22.62 g (91%) of the title compound as a light-yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (t, J = 7.1 Hz, 3H), 3.59 (s, 2H), 4.16 (q, J = 7.0 Hz, 2H), 7.23 (d, J = 8.2 Hz, 2H), 7.29 (d, J = 8.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 40.8, 61.1, 128.8, 130.7, 132.7, 133.1, 171.2.

Ethyl 2-(4-Methoxyphenyl)acetate.[19] Following the representative procedure, 20.77 g (125.0 mmol) of 4-methoxyphenylacetic acid yielded 23.51 g (97%) of the title compound as a light-yellow oil: n_D^{21} = 1.5080 (lit.[20] n_D^{20} = 1.5064); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (t, J = 7.2 Hz, 3H), 3.55 (s, 2H), 3.76 (s, 3H), 4.14 (q, J = 7.1 Hz, 2H), 6.86 (d, J = 8.5 Hz, 2H), 7.20 (d, J = 8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 40.5, 55.1, 60.7, 113.9, 126.3, 130.2, 158.7, 171.8.

Ethyl 2-(4-Trifluoromethylphenyl)acetate.[21] Following the representative procedure, 20.42 g (100.0 mmol) of 4-trifluoromethylphenyl-

DOI: 10.1021/acs.joc.6b02428
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acetic acid gave 21.47 g (93%) of the title compound as a white crystalline solid: mp 37.1−38.2 °C (ethanol) (lit.[22] mp 34−35 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (t, J = 7.2 Hz, 3H), 3.67 (s, 2H), 4.17 (q, J = 7.2 Hz, 2H), 7.41 (d, J = 8.1 Hz, 2H), 7.58 (d, J = 8.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 41.3, 61.3, 124.3 (q, J_{C-F} = 272 Hz), 125.6 (q, J_{C-F} = 3.7 Hz), 129.6 (q, J_{C-F} = 32.5 Hz), 129.9, 138.3, 171.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.6.

Ethyl 2-(3,5-Bis(trifluoromethyl)phenyl)acetate.[23] Following the representative procedure, 34.02 g (125.0 mmol) of 3,5-bis-(trifluoromethyl)phenylacetic acid afforded 31.42 g (84%) of the title compound as a light-yellow oil: n_D^{21} = 1.4239; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (t, J = 7.2 Hz, 3H), 3.74 (s, 2H), 4.18 (q, J = 7.2 Hz, 2H), 7.76 (s, 2H), 7.79 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 40.8, 61.6, 121.5 (septet, J_{C-F} = 3.8 Hz), 123.5 (q, J_{C-F} = 272 Hz), 129.9 (q, J_{C-F} = 3.7 Hz), 132.0 (q, J_{C-F} = 33.2 Hz), 136.8, 170.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ −63.0; HRMS (DART-TOF) m/z calcd for $C_{12}H_{10}F_6O_2$ $[M + H]^+$ 301.0663, found 301.0677.

Ethyl 2-(4-Bromophenyl)acetate.[19] Following the representative procedure, 16.58 g (77.0 mmol) of 4-bromophenylacetic acid gave 16.55 g of the title compound as a clear, colorless oil that crystallized upon standing: mp 30.5−31.4 °C (ethanol) (lit.[24] mp 31−34 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (t, J = 7.2 Hz, 3H), 3.55 (s, 2H), 4.14 (q, J = 7.2 Hz, 2H), 7.15 (d, J = 8.3 Hz, 2H), 7.43 (d, J = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 40.8, 61.1, 121.1, 131.1, 131.7, 133.2, 171.0.

Synthesis of Diethyl Arylmalonates. *Diethyl (4-Bromophenyl)-malonate.*[19] Following the general method of Enoua and co-workers with minor modifications,[25] a dry 250 mL round-bottomed flask containing a magnetic stir bar was flushed with dry nitrogen and charged with 5.92 g (246.9 mmol) of oil-free sodium hydride, 150 mL of anhydrous THF, and 36.47 g (308.7 mmol) of diethyl carbonate. Carefully, 15.01 g (61.7 mmol) of ethyl 2-(4-bromophenyl)acetate in 40 mL of anhydrous THF was added dropwise over a period of 10 min. The flask was then fitted with a condenser, and the reaction mixture was heated at reflux. The reaction progress was monitored colorimetrically; the initial off-white solution developed a bright orange color over the course of the reaction, and upon persistence of this color (ca. 4 h for most substrates) the reaction was cooled to room temperature. An ice−water bath was placed under the reaction flask, and saturated, aqueous ammonium chloride was added dropwise through the condenser until the evolution of hydrogen gas ceased. The mixture was then poured into a 500 mL separatory funnel, and 100 mL of Et_2O was added. The organic layer was collected, and the aqueous layer was extracted with Et_2O (2 × 75 mL). The combined organic layers were rinsed with saturated, aqueous ammonium chloride (2 × 75 mL), saturated, aqueous $NaHCO_3$ (2 × 75 mL), and brine (1 × 50 mL), dried over Na_2SO_4, and concentrated. The resulting orange oil was distilled (Kugelrohr, bath temperature = 195 °C, 20 mm) to yield 17.50 g (90%) of the title compound as a colorless oil: n_D^{23} = 1.515; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (t, J = 7.2 Hz, 6H), 4.14−4.27 (m, 4H), 4.56 (s, 1H), 7.28 (d, J = 8.5 Hz, 2H), 7.48 (d, J = 8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 57.5, 62.1, 122.6, 131.2, 131.9, 132.0, 167.8.

Diethyl 2-(4-Trifluoromethylphenyl)malonate.[26] Following the representative procedure with minor modification, 10.00 g (43.0 mmol) of ethyl 2-(4-trifluoromethylphenyl)acetate afforded a light orange oil that was purified by passage through 50 g of silica gel with 15% Et_2O in pentane as eluent. Removal of the solvent under reduced pressure gave a light-yellow oil that crystallized upon standing. Recrystallization from 50 mL of pentane yielded 8.99 g (69%) of the title compound as a white crystalline solid: mp 28.6−29.0 °C (pentane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (t, J = 7.2 Hz, 6H), 4.16−4.29 (m, 4H), 4.68 (s, 1H), 7.54 (d, J = 8.2 Hz, 2H), 7.62 (d, J = 8.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 57.9, 62.3, 124.2 (q, J_{C-F} = 272 Hz), 125.6 (q, J_{C-F} = 3.7 Hz), 130.0, 130.6 (q, J_{C-F} = 32.6 Hz), 136.9, 167.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.8; HRMS (DART-TOF) m/z calcd for $C_{14}H_{15}F_3O_4$ $[M + H]^+$ 305.1001, found 305.0990.

Diethyl 2-(3,5-Bis(trifluoromethyl)phenyl)malonate.[27] Following the representative procedure with minor modification, 6.00 g (20.0 mmol) of ethyl 2-(3,5-bis(trifluoromethyl)phenyl)acetate afforded a crude yellow oil that was purified by passage through 40 g of silica gel using 20% ethyl acetate in hexanes as eluent. Removal of the solvent afforded 6.30 g (85%) of the title compound as a light-yellow oil: n_D^{21} = 1.4250; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, J = 7.1 Hz, 6H), 4.16−4.32 (m, 4H), 4.74 (s, 1H), 7.86 (s, 1H), 7.91 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 57.6, 62.7, 122.5 (apparent septet, J_{C-F} = 3.7 Hz), 123.3 (q, J_{C-F} = 272 Hz), 130.0 (apparent q, J_{C-F} = 3.6 Hz), 132.0 (q, J_{C-F} = 33.5 Hz), 135.3, 167.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.9; HRMS (DART-TOF) m/z calcd for $C_{15}H_{14}F_6O_4$ $[M + H]^+$ 373.0875, found 373.0867.

Diethyl 2-(4-Methoxyphenyl)malonate.[27] Following the representative procedure, with the modification that the reaction mixture was heated at reflux for 7 h before workup, 7.50 g (38.6 mmol) of ethyl 2-(4-methoxyphenyl)acetate afforded a light-yellow oil that was purified by column chromatography (100 g SiO_2, 0 → 10% Et_2O/hexanes; the product eluted in fractions after 6% Et_2O/hexanes) to yield 6.20 g (60%) of the title compound as a colorless oil: n_D^{20} = 1.4975 (lit.[28] n_D^{20} = 1.4988); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (t, J = 7.1 Hz, 6H), 3.80 (s, 3H), 4.14−4.28 (m, 4H), 4.55 (s, 1H), 6.89 (d, J = 8.7 Hz, 2H), 7.32 (d, J = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 55.5, 57.4, 61.9, 114.2, 125.2, 130.59, 159.7, 168.6.

Diethyl 2-(4-Chlorophenyl)malonate. Following the procedure of Meyer and Levene for the synthesis of diethyl phenylmalonate,[29] 20.99 g (106 mmol) of ethyl 2-(4-chlorophenyl)acetate afforded 8.65 g (30%) of the title compound as a colorless oil after distillation: bp 175−180 °C (10 mm) [lit.[25] bp 170−180 °C (27 mbar)]; n_D^{21} = 1.4970 (lit.[30] n_D^{25} = 1.4999); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (t, J = 7.1 Hz, 6H), 4.10−4.27 (m, 4H), 4.58 (s, 1H), 7.30−7.36 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 57.4, 62.1, 128.9, 130.8, 131.4, 134.4, 167.9.

Synthesis of 2-Aryl-1,3-propanediols. *2-(4-Trifluoromethyl-phenyl)-1,3-propanediol.*[26] A solution of 6.95 g (22.8 mmol) of diethyl (4-trifluoromethylphenyl)malonate in 50 mL of dry Et_2O was added to a 0 °C suspension of 1.30 g (34.2 mmol) of lithium aluminum hydride in 150 mL of Et_2O. The resulting mixture was stirred at room temperature overnight and then hydrolyzed by sequential, dropwise addition of 1.5 mL of water, 1.5 mL of a 1 M aqueous solution of sodium hydroxide, and 6 mL of water. The mixture was filtered through a pad of Celite and the solids were washed with three 150 mL portions of Et_2O. The combined filtrate and washings were dried (Na_2SO_4) and concentrated under reduced pressure to yield a thick oil which was purified by column chromatography (100 g SiO_2, 15 → 80% Et_2O/pentane, product eluted in fractions after 60% Et_2O/pentane). Combining relevant fractions and removal of the solvent yielded a solid which was recrystallized from pentane to afford 2.79 g (56%) of the title compound as a white crystalline solid: mp 48.8−50.0 °C (pentane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.75 (br s, 2H), 3.05−3.18 (m, 1H), 3.87−4.04 (m, 4H), 7.34 (d, J = 7.8 Hz, 2H), 7.57 (d, J = 7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 49.6, 65.6, 124.3 (q, J_{C-F} = 272 Hz), 125.8 (apparent q, J_{C-F} = 3.6 Hz), 128.7, 129.7 (q, J_{C-F} = 32.5 Hz), 144.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.6; HRMS (DART-TOF) m/z calcd for $C_{10}H_{11}F_3O_2$ $[M + H]^+$ 221.0789, found 221.0800.

2-(4-Bromophenyl)-1,3-propanediol.[19] A solution of 15.80 g (50.1 mmol) of diethyl (4-bromophenyl)malonate in 75 mL of dry Et_2O was reduced with 2.85 g (75.2 mmol) of lithium aluminum hydride in 150 mL of Et_2O. The reaction mixture was worked up as described above, the solids were extracted overnight with Et_2O using a Soxhlet extractor, and the resulting oil was purified by column chromatography (100 g SiO_2, 20 → 100% Et_2O/pentane, product eluted in fractions after 60% Et_2O/pentane). The clear oil obtained after solvent removal crystallized upon standing and was recrystallized from pentane/Et_2O to afford 5.50 g (48%) of the title compound as a white crystalline solid: mp 65.8−66.5 °C (pentane/Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44 (br s, 2H), 3.02 (quintet, J = 6.4 Hz, 1H), 3.89 (dd, J = 10.7 Hz, J = 5.5 Hz, 2H), 4.02 (dd, J = 10.7 Hz, J = 7.6 Hz, 2H), 7.11 (d, J = 8.4 Hz, 2H), 7.45 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 49.3, 65.8,121.2, 130.0, 132.1, 138.7; HRMS (DART-TOF) m/z calcd for $C_9H_{11}BrO_2$ $[M + H]^+$ 231.0021, found 231.0042.

DOI: 10.1021/acs.joc.6b02428
J. Org. Chem. 2016, 81, 12116−12127

2-Phenyl-1,3-propanediol.[31] A solution of 5.91 g (25.0 mmol) of diethyl phenylmalonate in 20 mL of dry Et_2O was reduced with 1.42 g (37.5 mmol) of lithium aluminum hydride in 100 mL of Et_2O. The reaction mixture was worked up as described above to afford an oil that crystallized upon standing. The solid was triturated with pentane to yield 3.18 g (84%) of the title compound: mp 51.8−52.3 °C (pentane) (lit.[3] mp 50−51.5 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.59 (br s, 2H), 3.02−3.12 (m, 1H), 3.86−4.03 (m, 4H), 7.22 (d, J = 7.3 Hz, 2H), 7.26 (t, J = 7.3 Hz, 1H), 7.33 (t, J = 7.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 49.9, 66.2,127.4, 128.2, 129.0, 139.5.

2-(3,5-Bis(trifluoromethyl)phenyl)-1,3-propanediol. A solution of 5.00 g (13.4 mmol) of diethyl (3,5-bis(trifluoromethyl)phenyl)-malonate in 50 mL of dry Et_2O was reduced with 765 mg (20.2 mmol) of lithium aluminum hydride in 150 mL of Et_2O. The reaction mixture was worked up as described above, and the resulting yellow oil was purified by column chromatography (25 g SiO_2, 20% ethyl acetate/pentane then 70% ethyl acetate/pentane, product eluted in fractions after the addition of 70% ethyl acetate/pentane) to yield a clear oil after solvent removal, which when triturated with $CHCl_3$, crystallized upon standing to afford 762 mg (20%) of the title compound: mp 66.3−67.2 °C ($CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 (br s, 2H), 3.17 (quintet, J = 6.0 Hz, 1H), 4.00 (dd, J = 10.7 Hz, J = 5.5 Hz, 2H), 4.02 (dd, J = 10.7 Hz, J = 6.6 Hz, 2H), 7.74 (s, 2H), 7.78 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 49.2, 64.9, 121.3 (apparent septet, J_{C-F} = 3.8 Hz), 123.5 (q, J_{C-F} = 272 Hz), 128.6 (apparent q, J_{C-F} = 3.4 Hz), 132.0 (q, J_{C-F} = 33.1 Hz), 142.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.9; HRMS (DART-TOF) m/z calcd for $C_{11}H_{10}F_6O_2$ $[M + H]^+$ 289.0663, found 289.0662.

2-(4-Methoxyphenyl)-1,3-propanediol.[19] A solution of 6.20 g (23.3 mmol) of diethyl (4-methoxyphenyl)malonate in 50 mL of dry Et_2O was reduced with 3.56 g (93.1 mmol) of lithium aluminum hydride in 150 mL of Et_2O. The reaction mixture was worked up as described above, and the resulting solid was recrystallized from Et_2O/pentane to yield 2.88 g (68%) of the title compound as a white solid: mp 83.6−84.5 °C (Et_2O/pentane) (lit.[32] mp 83−85 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.80 (br s, 2H), 3.06 (quintet, J = 6.62 Hz, 1H), 3.80 (s, 3H), 3.91 (dd, J = 10.7 Hz, J = 5.7 Hz, 2H), 3.97 (dd, J = 10.7 Hz, J = 7.5 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 7.16 (d, J = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 49.3, 55.5, 66.43, 114.4, 129.2, 131.3, 159.0.

2-(2-Pyridyl)-1,3-propanediol.[33] Following a modification of the procedure of Lipp and Richard,[34] 14.0 mL (101 mmol) of 2-picoline and 33.2 mL (404 mmol) of a 37 wt % solution of formaldehyde in water was heated at reflux for 48 h. After the mixture was cooled to room temperature, 50 mL of methanol was added to the reaction flask and solvent was removed via rotary evaporation; the process was repeated three times. Then 50 mL of cyclohexane was added to the flask, and the volatile components were removed by rotary evaporation; this process was also repeated three times. The resulting dark brown, viscous oil was purified by column chromatography (100 g SiO_2, 0 → 100% ethanol/ethyl acetate, product eluted after the addition of 40% ethanol/ethyl acetate) to yield 2.07 g (13%) of the title compound as a clear oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.04 (quintet, J = 5.3 Hz, 1H), 3.95 (dd, J = 11.0 Hz, J = 5.0 Hz, 2H), 4.04 (dd, J = 11.0 Hz, J = 5.7 Hz, 2H), 4.4 (br s, 2H), 7.14 (dd, J = 7.3 Hz, J = 5.0 Hz, 1H), 7.21 (d, J = 7.8 Hz, 1H), 7.62 (td, J = 7.6 Hz, J = 1.7 Hz, 1H) 8.42 (br d, J = 4.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 49.7, 63.6, 122.2, 123.8, 137.1, 148.7, 161.7; HRMS (DART-TOF) m/z calcd for $C_8H_{11}NO_2$ $[M + H]^+$ 154.0868, found 154.0838.

Synthesis of 5-Aryl-1,3-dioxanes. *cis-2-Isopropyl-5-phenyl-1,3-dioxane (1) and trans-2-Isopropyl-5-phenyl-1,3-dioxane (2).* A mixture of 3.18 g (20.8 mmol) of 2-phenyl-1,3-propanediol, 3.00 g (41.6 mmol) of isobutyraldehyde, and 100 mg of p-TsOH in 35 mL of cyclohexane was stirred at 40 °C for 1.5 h and then was heated at reflux under a Dean−Stark trap for 4 h. The reaction mixture was allowed to cool to room temperature, 500 mg of anhydrous K_2CO_3 was added, and the mixture was transferred to a separatory funnel, washed with basic water (pH ∼ 9, 3 × 50 mL) and brine (1 × 50 mL), and dried (Na_2SO_4). The solvent was removed by rotary evaporation to yield 2.54 g of a light-yellow oil. A 370 mg portion of the product mixture was separated using an autoflash column [40 g of prepacked SiO_2 (40−60 μm, 60 Å)] with a gradient program 0 → 4% Et_2O/hexanes over the course of 45 min: 5 mL fractions were collected; fractions 9−15 were enriched in the minor cis isomer (**1**), and pure *trans*-isomer (**2**) was collected in fractions 17−22. Concentration of fractions 17−22 afforded 140 mg (43%) of pure **2**. Fractions 9−15 were combined and concentrated, and the resulting oil was taken up in 350 μL of CH_2Cl_2. Pure cis isomer (**1**), 4.0 mg (ca. 2%), was isolated from this solution by preparative GC on a 10 ft × 0.25 in. 20% SE-30 on an Anakrom (60−70 mesh) column using He as the carrier gas at a flow rate of 175 mL/min and an oven temperature of 170 °C: retention time of the cis isomer (**1**) was 14.7 min and the trans isomer (**2**) was 16.3 min. This process was repeated as additional isomerically pure material was needed. The isomers **1** and **2** were distinguished using two-dimensional ^{1}H NOESY techniques as detailed in the Supporting Information.

cis-2-Isopropyl-5-phenyl-1,3-dioxane (1): colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.98 (d, J = 6.8 Hz, 6H), 1.85−1.92 (m, 1H), 2.58−2.64 (br m, 1H), 4.17 (dd, J = 11.5 Hz, J = 3.1 Hz, 2H), 4.21 (t, J = 11.6 Hz, 2H), 4.41 (d, J = 4.6 Hz, 1H), 7.24 (t, J = 7.5 Hz, 1H), 7.32 (t, J = 7.5 Hz, 2H), 7.56 (d, J = 7.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.1, 33.1, 39.7, 71.3, 106.2, 126.6, 128.5, 128.7, 143.6; HRMS (DART-TOF) m/z calcd for $C_{13}H_{18}O_2$ $[M + H]^+$ 207.1385, found 207.1398.

trans-2-Isopropyl-5-phenyl-1,3-dioxane (2): colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (d, J = 6.9 Hz, 6H), 1.82−1.94 (m, 1H), 3.20 (tt, J = 11.6 Hz, J = 4.5 Hz, 1H), 3.81 (t, J = 11.6 Hz, 2H), 4.22 (dd, J = 11.6 Hz, J = 4.5 Hz), 4.34 (d, J = 5.0 Hz, 1H), 7.18 (d, J = 7.1 Hz, 2H), 7.26 (t, J = 7.4 Hz, 1H), 7.33 (t, J = 7.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.3, 32.9, 41.6, 72.2, 106.0, 127.5, 127.9, 128.9, 138.2; HRMS (DART-TOF) m/z calcd for $C_{13}H_{18}O_2$ $[M + H]^+$ 207.1385, found 207.1390.

cis-2-tert-Butyl-5-(4-chlorophenyl)-1,3-dioxane (3) and trans-2-tert-Butyl-5-(4-chlorophenyl)-1,3-dioxane (4). A solution of 5.00 g (29.3 mmol) of diethyl (4-chlorophenyl)malonate in 20 mL of dry Et_2O was reduced with 1.67 g (43.9 mmol) of lithium aluminum hydride in 100 mL of Et_2O. The reaction mixture was worked up as described above to give 2.32 g of 2-(4-chlorophenyl)-1,3-propanediol. The crude diol, 2.14 g (24.9 mmol) of pivaldehyde, and 237 mg of p-TsOH in 40 mL of cyclohexane were heated at reflux under a Dean−Stark trap for 12 h. The reaction mixture was allowed to cool to room temperature, 0.5 g of anhydrous K_2CO_3 was added, and the mixture was stirred for 30 min, transferred to a separatory funnel with 50 mL of Et_2O, washed with basic water (pH ∼9, 2 × 25 mL) and brine (1 × 25 mL), and dried (Na_2SO_4). The solvent was removed by rotary evaporation to give 2.58 g of a light-yellow oil that was taken up in pentane, loaded onto 200 g of neutral alumina, and purified via flash chromatography (0 → 5% Et_2O/pentane); 25 mL fractions were collected. Fractions 14−31, containing the isomers of interest, were concentrated to afford 1.34 g of a white solid. GC analysis revealed that material consisted of the *trans*- (**4**) and *cis*-dioxanes (**3**) in an approximately 4:1 ratio. Separation of the isomers was achieved by preparative TLC of a 50 mg portion of the mixture on a 1000 μm SiO_2 glass-backed plate using a 5% solution of ethyl acetate in hexanes as an eluent to give 8.0 mg (16%) of **3** (R_f = 0.44) and 40 mg (80%) of **4** (R_f = 0.53). This process was repeated as additional isomerically pure material was needed. Isomers **3** and **4** were distinguished using two-dimensional ^{1}H NOESY techniques as detailed in the Supporting Information. Each of the isomers was recrystallized, as described below, to give analytical samples used in the equilibration and crystallographic studies.

cis-2-tert-Butyl-5-(4-chlorophenyl)-1,3-dioxane (3): colorless solid; mp 65.7−66.6 °C (pentane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (s, 9H), 2.54−2.58 (br m, 1H), 4.10−4.20 (m, 4H), 4.23 (s, 1H), 7.28 (d, J = 8.4 Hz, 2H), 7.50 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.9, 35.4, 39.2, 71.3, 108.4, 128.5, 130.2, 132.4, 142.2; HRMS (DART-TOF) m/z calcd for $C_{14}H_{19}ClO_2$ $[M - H]^+$ 253.0995, found 253.1016.

trans-2-tert-Butyl-5-(4-chlorophenyl)-1,3-dioxane (4): white solid; mp 72.8−73.9 °C (pentane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (s,

DOI: 10.1021/acs.joc.6b02428
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9H), 3.15 (tt, J = 11.3 Hz, J = 4.6 Hz, 1H), 3.74 (t, J = 11.5 Hz, 2H), 4.17 (s, 1H), 4.18 (dd, J = 11.6 Hz, J = 4.6 Hz), 7.11 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.0, 35.0, 41.0, 72.1, 108.0, 129.1, 129.2, 133.3, 136.7; HRMS (DART-TOF) m/z calcd for $C_{14}H_{19}ClO_2$ $[M - H]^+$ 253.0995, found 253.0981.

*cis-5-(4-Bromophenyl)-2-tert-butyl-1,3-dioxane (**5**) and trans-5-(4-Bromophenyl)-2-tert-butyl-1,3-dioxane (**6**).* A mixture of 5.02 g (21.8 mmol) of 2-(4-bromophenyl)-1,3-propanediol, 4.70 g (54.6 mmol) of pivaldehyde, and 123 mg of *p*-TsOH in 30 mL of benzene was stirred at room temperature for 30 min and then gradually heated over a period of 5 h and held at reflux under a Dean−Stark trap for 12 h. The reaction mixture was allowed to cool to room temperature, 500 mg of anhydrous K_2CO_3 was added, and the mixture was stirred for 30 min, transferred to a separatory funnel with 100 mL of Et_2O, washed with basic water (pH ∼9, 2 × 50 mL) and brine (1 × 50 mL), and dried (Na_2SO_4). The solvent was removed by rotary evaporation, and the residue was taken up in a solution of 40% Et_2O/pentane and passed through a short bed of SiO_2. Solvent was removed by rotary evaporation to give 6.27 g (96%) of a mixture of **5** and **6**. Separation of compounds **5** and **6** was achieved by preparative TLC of a 52 mg portion of the mixture on a 1000 μm SiO_2 glass-backed plate using a 6% solution of Et_2O in pentane as an eluent to give 9.3 mg (18%) of **5** (R_f = 0.51) and 28 mg of **6** (R_f = 0.68). This process was repeated as additional isomerically pure material was needed. Isomers **5** and **6** were distinguished using two-dimensional ^{1}H NOESY techniques as detailed in the Supporting Information. Each of the isomers was recrystallized as described below to give analytical samples used in the equilibration studies.

*cis-5-(4-Bromophenyl)-2-tert-butyl-1,3-dioxane (**5**):* colorless solid; mp 60.6−61.5 °C (pentane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (s, 9H), 2.52−2.56 (br m, 1H), 4.12−4.16 (m, 4H), 4.23 (s, 1H), 7.42−7.46 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.9, 35.4, 39.2, 71.3, 108.4, 120.5, 130.6, 131.4, 142.7; HRMS (DART-TOF) m/z calcd for $C_{14}H_{19}BrO_2$ $[M + H]^+$ 299.0647, found 299.0652.

*trans-5-(4-Bromophenyl)-2-tert-butyl-1,3-dioxane (**6**):* white solid; mp 71.5−72.3 °C (pentane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (s, 9H), 3.13 (tt, J = 11.3 Hz, J = 4.6 Hz, 1H), 3.73 (t, J = 11.5 Hz, 2H), 4.17 (s, 1H), 4.18 (dd, J = 11.6 Hz, J = 4.5 Hz), 7.05 (d, J = 8.3 Hz, 2H), 7.44 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.0, 35.0, 41.1, 72.0, 108.0, 121.3, 129.5, 132.1, 137.2; HRMS (DART-TOF) m/z calcd for $C_{14}H_{19}BrO_2$ $[M + H]^+$ 299.0647, found 299.0617.

*cis-2-tert-Butyl-5-(4-trifluoromethylphenyl)-1,3-dioxane (**7**) and trans-2-tert-Butyl-5-(4-trifluoromethylphenyl)-1,3-dioxane (**8**).* A mixture of 1.72 g (10.0 mmol) of 2-(4-trifluoromethylphenyl)-1,3-propanediol, 4.70 g (54.6 mmol) of pivaldehyde, and 75 mg of *p*-TsOH in 20 mL of benzene was stirred at room temperature for 30 min and then gradually heated over a period of 5 h and held at reflux under a Dean−Stark trap for 12 h. The reaction mixture was allowed to cool to room temperature, 0.5 g of anhydrous K_2CO_3 was added, and the mixture was stirred for 30 min, transferred to a separatory funnel with 50 mL of Et_2O, washed with basic water (pH ∼8, 3 × 50 mL) and brine (1 × 50 mL), and dried (Na_2SO_4). The solvent was removed by rotary evaporation to yield a clear oil that crystallized upon standing. Separation of compounds **7** and **8** was achieved by preparative TLC of a 72 mg portion of the mixture on a 1000 μm SiO_2 glass-backed plate using an 8% solution of Et_2O in pentane as eluent to give 12 mg (17%) of **7** (R_f = 0.50) and 51 mg (71%) of **8** (R_f = 0.71). This process was repeated as additional isomerically pure material was needed. Isomers **7** and **8** were distinguished using two-dimensional ^{1}H NOESY techniques as detailed in the Supporting Information. Each of the isomers was recrystallized, as described below, to give analytical samples used in the equilibration studies.

*cis-2-tert-Butyl-5-(4-trifluoromethylphenyl)-1,3-dioxane (**7**):* colorless solid; mp 37.1−38.0 °C (pentane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (s, 9H), 2.62−2.68 (br m, 1H), 4.14−4.24 (m, 4H), 4.25 (s, 1H), 7.57 (d, J = 8.1 Hz, 2H), 7.69 (d, J = 8.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.9, 35.4, 39.6, 71.1, 108.5, 124.5 (q, J_{C-F} = 272 Hz), 125.3 (q, J_{C-F} = 3.8 Hz), 128.9 (q, J_{C-F} = 32.5 Hz), 129.1, 147.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.5; HRMS (DART-TOF) m/z calcd for $C_{15}H_{19}F_3O_2$ $[M - H]^+$ 287.1259, found 287.1286.

*trans-2-tert-Butyl-5-(4-trifluoromethylphenyl)-1,3-dioxane (**8**):* white solid; mp 87.1−87.9 °C (CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (s, 9H), 3.24 (tt, J = 11.3 Hz, J = 4.6 Hz, 1H), 3.79 (t, J = 11.5 Hz, 2H), 4.19 (s, 1H), 4.21 (dd, J = 11.6 Hz, J = 4.6 Hz, 2H), 7.29 (d, J = 8.1 Hz, 2H), 7.58 (d, J = 8.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.0, 35.1, 41.5, 71.9, 108.1, 124.3 (q, J_{C-F} = 272 Hz), 125.9 (q, J_{C-F} = 3.7 Hz), 128.3, 129.8 (q, J_{C-F} = 32.6 Hz), 129.1, 142.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.7; HRMS (DART-TOF) m/z calcd for $C_{15}H_{19}F_3O_2$ $[M - H]^+$ 287.1259, found 287.1286.

*cis-2-tert-Butyl-5-(3,5-bis(trifluoromethyl)phenyl)-1,3-dioxane (**9**) and trans-2-tert-Butyl-5-(3,5-bis(trifluoromethyl)phenyl)-1,3-dioxane (**10**).* A mixture of 709 mg (2.46 mmol) of 2-(3,5-bis(trifluoromethyl)phenyl)-1,3-propanediol, 423 mg (4.92 mmol) of pivaldehyde, and 53 mg of *p*-TsOH in 20 mL of benzene was stirred at room temperature for 30 min and then gradually heated over a period of 5 h and held at reflux under a Dean−Stark trap for 12 h. The reaction mixture was allowed to cool to room temperature, 500 mg of anhydrous K_2CO_3 was added, and the mixture was stirred for 30 min, transferred to a separatory funnel with 50 mL of Et_2O, washed with basic water (pH ∼8, 3 × 25 mL) and brine (1 × 25 mL), and dried (Na_2SO_4). The solvent was removed by rotary evaporation to yield 837 mg (96%) of the title compounds as a mixture of isomers. Separation of isomers **9** and **10** was achieved by column chromatography (150 g SiO_2, 0 → 10% Et_2O/pentane); 25 mL fractions were collected: once material started to elute (ca. 4% Et_2O/pentane), 25 mg (3%) of pure *trans*-isomer (**10**) was collected in fractions 1 and 2; 106 mg (13%) of pure *cis*-isomer (**9**) was collected in fractions 12−14. Additionally, fractions 3−11, which contained a mixture of **9** and **10**, were combined, and further separation was effected by preparative TLC of a 71 mg portion of the mixture on a 1000 μm SiO_2 glass-backed plate using a 10% solution of Et_2O in pentane as eluent. From this sample, an additional 21 mg (30%) of **9** (R_f = 0.67) and 39 mg (55%) of **10** (R_f = 0.87) was isolated. This process was repeated as additional isomerically pure material was needed. Isomers **9** and **10** were distinguished using two-dimensional ^{1}H NOESY techniques as detailed in the Supporting Information. Each of the isomers was recrystallized, as described below, to give analytical samples used in the equilibration studies.

*cis-2-tert-Butyl-5-(3,5-bis(trifluoromethyl)phenyl)-1,3-dioxane (**9**):* white solid; mp 44.2−45.1 °C (CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (s, 9H), 2.71−2.75 (m, 1H), 4.14−4.24 (m, 4H), 4.28 (s, 1H), 7.77 (s, 1H), 8.10 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.8, 35.4, 39.6, 70.8, 108.6, 120.7 (septet, J_{C-F} = 3.8 Hz), 123.7 (q, J_{C-F} = 273 Hz), 129.3 (apparent quartet, J_{C-F} = 2.6 Hz), 131.5 (q, J_{C-F} = 33.0 Hz), 146.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.8; HRMS (DART-TOF) m/z calcd for $C_{16}H_{18}F_6O_2$ $[M - H]^+$ 355.1133, found 355.1146.

*trans-2-tert-Butyl-5-(3,5-bis(trifluoromethyl)phenyl)-1,3-dioxane (**10**):* white solid; mp 98.6−99.5 °C (CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (s, 9H), 3.32 (tt, J = 11.3 Hz, J = 4.6 Hz, 1H), 3.81 (t, J = 11.4 Hz, 2H), 4.22 (s, 1H), 4.24 (dd, J = 11.6 Hz, J = 4.6 Hz, 2H), 7.62 (s, 2H), 7.78 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.9, 35.1, 41.4, 71.6, 108.1, 121.6 (septet, J_{C-F} = 3.8 Hz), 123.4 (q, J_{C-F} = 273 Hz), 128.1 (apparent quartet, J_{C-F} = 2.7 Hz), 132.4 (q, J_{C-F} = 33.3 Hz), 140.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ −63.0; HRMS (DART-TOF) m/z calcd for $C_{16}H_{18}F_6O_2$ $[M - H]^+$ 355.1133, found 355.1145.

*cis-2-tert-Butyl-5-(4-methoxyphenyl)-1,3-dioxane (**11**) and trans-2-tert-Butyl-5-(4-methoxyphenyl)-1,3-dioxane (**12**).* A mixture of 5.68 g (31.2 mmol) of 2-(4-methoxyphenyl)-1,3-propanediol, 5.37 g (62.4 mmol) of pivaldehyde, and 125 mg of *p*-TsOH in 40 mL of benzene was stirred at room temperature for 30 min and then gradually heated over a period of 5 h and held at reflux under a Dean−Stark trap for 4 h. The reaction mixture was allowed to cool to room temperature, 500 mg of anhydrous K_2CO_3 was added, and the mixture was stirred for 30 min, transferred to a separatory funnel with 100 mL of Et_2O, washed with basic water (pH ∼8, 3 × 50 mL), brine (1 × 50 mL), and dried (Na_2SO_4). The solvent was removed by rotary

DOI: 10.1021/acs.joc.6b02428
J. Org. Chem. 2016, 81, 12116−12127

evaporation to yield 4.33 g (56%) of the title compounds as a mixture of isomers. A 103 mg portion of this mixture was dissolved in 300 μL of Et_2O. Pure cis isomer (**11**), 2.2 mg (2%), and pure trans isomer (**12**), 26.6 mg (26%), were isolated from this solution by preparative GC on a 10 ft × 0.25 in. 20% SE-30 on an Anakrom (60−70 mesh) column using He as the carrier gas at a flow rate of 175 mL/min and an oven temperature of 200 °C: retention time of the cis isomer (**11**) was 27.5 min and the trans isomer (**12**) was 33.2 min. This process was repeated as additional isomerically pure material was needed. Isomers **11** and **12** were distinguished using two-dimensional ^{1}H NOESY techniques as detailed in the Supporting Information. The solid trans isomer (**12**) was recrystallized from CH_2Cl_2; analytically pure samples were used in the equilibration studies.

*cis-2-tert-Butyl-5-(4-methoxyphenyl)-1,3-dioxane (**11**):* colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (s, 9H), 2.51−2.56 (br m, 1H), 3.80 (s, 3H), 4.10−4.20 (m, 4H), 4.23 (s, 1H), 6.86 (d, J = 8.8 Hz, 2H), 7.48 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.0, 35.4, 39.0, 55.5, 71.7, 108.4, 113.8, 129.7, 136.1, 158.4; HRMS (DART-TOF) m/z calcd for $C_{15}H_{22}O_3$ $[M - H]^+$ 249.1491, found 249.1476.

*trans-2-tert-Butyl-5-(4-methoxyphenyl)-1,3-dioxane (**12**):* white solid; mp 58.3−59.1 °C (CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (s, 9H), 3.11 (tt, J = 11.4 Hz, J = 4.7 Hz, 1H), 3.74 (t, J = 11.5 Hz, 2H), 3.79 (s, 3H), 4.17 (s, 1H), 4.18 (dd, J = 11.7 Hz, J = 4.7 Hz, 2H), 6.86 (d, J = 8.7 Hz, 2H), 7.10 (d, J = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.1, 35.0, 40.7, 55.5, 72.5, 108.0, 114.4, 128.8, 130.3, 159.0; HRMS (DART-TOF) m/z calcd for $C_{15}H_{22}O_3$ $[M - H]^+$ 249.1491, found 249.1473.

*cis-2-tert-Butyl-5-(4-trimethylsilylphenyl)-1,3-dioxane (**13**) and trans-2-tert-Butyl-5-(4-trimethylsilylphenyl)-1,3-dioxane (**14**).* Under an atmosphere of dry argon, a solution of 1.50 g (5.00 mmol) of an isomeric mixture of **5** and **6** in 25 mL of anhydrous Et_2O was cooled to −78 °C, and 6.00 mL (12.0 mmol) of a 2.00 M solution of *t*-BuLi in heptane was added over a period of 5 min. The mixture was stirred for an additional 10 min at −78 °C, allowed to warm to room temperature, and stirred for 30 min. A separate flask was charged with a solution of 597 mg (5.50 mmol) of trimethylsilyl chloride in 25 mL of anhydrous Et_2O. The orange reaction mixture was then transferred dropwise by cannula into the flask containing the TMSCl solution. The reaction mixture was stirred for 30 min at room temperature, 20 mL of saturated, aqueous $NaHCO_3$ was added, and the contents were transferred to a separatory funnel. The organic layer was separated, the aqueous layer extracted with Et_2O (2 × 25 mL), and the combined organic layers were washed with water (2 × 25 mL) and brine (1 × 25 mL) and dried (K_2CO_3). Benzene (25 mL) was added, and solvent was removed under reduced pressure; this process was repeated twice to azeotropically remove heptane. Upon standing, the resulting clear oil crystallized to yield 1.42 g (97%) of a white crystalline solid. Preparative TLC of a 50 mg portion of this mixture on a 1000 μm SiO_2 glass-backed plate using a 6% solution of Et_2O in pentane as eluent afforded 26 mg (52%) of pure **14** (R_f = 0.80). Pure cis isomer (**13**), 5.0 mg (ca. 2.5%), was isolated from a 205 mg portion of the product mixture by preparative GC on a 10 ft × 0.25 in. 20% SE-30 on an Anakrom (60−70 mesh) column using He as the carrier gas at a flow rate of 175 mL/min and an oven temperature of 200 °C: retention time of the cis isomer (**13**) was 31.8 min and the trans isomer (**14**) was 38.3 min. This process was repeated as additional isomerically pure material was needed. Isomers **13** and **14** were distinguished using two-dimensional ^{1}H NOESY techniques as detailed in the Supporting Information. The solid trans isomer (**14**) was recrystallized from pentane; analytically pure samples were used in the equilibration studies.

*cis-2-tert-Butyl-5-(4-trimethylsilylphenyl)-1,3-dioxane (**13**):* colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.26 (s, 9H), 0.96 (s, 9H), 2.55−2.59 (br m, 1H), 4.13−4.23 (m, 4H), 4.24 (s, 1H), 7.48 (d, J = 8.0 Hz, 2H), 7.55 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −0.9, 25.0, 35.4, 39.8, 71.4, 108.4, 128.2, 133.5, 138.1, 144.4; HRMS (DART-TOF) m/z calcd for $C_{17}H_{28}O_2Si$ $[M + H]^+$ 293.1937, found 293.1934, m/z calcd for $C_{17}H_{28}O_2Si$ $[M - H]^+$ 291.1780, found 291.1767.

*trans-2-tert-Butyl-5-(4-trimethylsilylphenyl)-1,3-dioxane (**14**):* white solid; mp 87.9−88.6 °C (pentane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.28 (s, 9H), 0.98 (s, 9H), 3.18 (tt, J = 11.4 Hz, J = 4.6 Hz, 1H), 3.81 (t, J = 11.4 Hz, 2H), 4.21 (s, 1H), 4.23 (dd, J = 11.6 Hz, J = 4.5 Hz, 2H), 7.19 (d, J = 7.8 Hz, 2H), 7.50 (d, J = 7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −0.9, 25.1, 35.0, 41.6, 72.3, 108.0, 127.4, 134.0, 138.8, 139.6; HRMS (DART-TOF) m/z calcd for $C_{17}H_{28}O_2Si$ $[M + H]^+$ 293.1937, found 293.1905, m/z calcd for $C_{17}H_{28}O_2Si$ $[M - H]^+$ 291.1780, found 291.1778

*cis-2-tert-Butyl-5-(2-pyridyl)-1,3-dioxane (**15**) and trans-2-tert-Butyl-5-(2-pyridyl)-1,3-dioxane (**16**).* A mixture of 1.78 g (11.6 mmol) of 2-(2-pyridyl)-1,3-propanediol, 2.00 g (23.3 mmol) of pivaldehyde, and 2.43 g (12.8 mmol) of *p*-TsOH in 40 mL of cyclohexane was stirred at room temperature for 1.5 h and then held at reflux under a Dean−Stark trap for 12 h. The reaction mixture was allowed to cool to room temperature, 1.5 g of anhydrous K_2CO_3 was added, and the mixture was stirred for 1.5 h, transferred to a separatory funnel with 100 mL of Et_2O, rinsed with a solution of saturated, aqueous Na_2CO_3 (2 × 25 mL), washed with basic water (pH ∼ 8, 3 × 50 mL) and brine (1 × 50 mL), and dried (Na_2SO_4).The solvent was removed by rotary evaporation to give 2.95 g of a light-yellow oil that was dissolved in pentane and loaded onto 250 g of neutral alumina. The column was eluted using a gradient (0 → 10% Et_2O/pentane); 30 mL fractions were collected: 123 mg (5%) of pure trans isomer (**16**) was collected in fractions 19−22; 369 mg (14%) of of pure cis isomer (**15**) was collected in fractions 26−28. Isomers **15** and **16** were distinguished using two-dimensional ^{1}H NOESY techniques as detailed in the Supporting Information. Each of the isomers was recrystallized, as described below, to give analytically pure samples.

*cis-2-tert-Butyl-5-(2-pyridyl)-1,3-dioxane (**15**):* white solid; mp 44.8−45.4 °C (pentane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (s, 9H), 2.78−2.82 (br m, 1H), 4.17 (br d, J = 11.5 Hz, 2H), 4.25 (s, 1H), 4.38 (d, J = 11.5 Hz, 2H), 7.14 (t, J = 5.5 Hz, 1H), 7.65 (tt, J = 7.7 Hz, J = 2.0 Hz, 1H), 7.85 (d, J = 8.0 Hz, 1H), 8.52 (br d, J = 4.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.9, 35.3, 42.2, 70.2, 108.3, 121.7, 123.2, 136.4, 149.1, 162.5; HRMS (DART-TOF) m/z calcd for $C_{13}H_{19}NO_2$ $[M + H]^+$ 222.1489, found 222.1480.

*trans-2-tert-Butyl-5-(2-pyridyl)-1,3-dioxane (**16**):* white solid; mp 71.5−72.3 °C (pentane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (s, 9H), 3.30 (tt, J = 11.1 Hz, J = 4.6 Hz, 1H), 3.99 (t, J = 11.4 Hz, 2H), 4.20 (s, 1H), 4.26 (dd, J = 11.5 Hz, J = 4.6 Hz, 2H), 7.12 (apparent t, J = 6.5 Hz, 2H) 7.13 (dd, J = 7.6 Hz, J = 5.2 Hz, 2H), 7.59 (td, J = 7.6 Hz, J = 1.7 Hz, 1H), 8.52 (br d, J = 4.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.0, 35.0, 43.1, 71.3, 107.9, 122.2, 123.32, 136.7, 149.7, 158.5; HRMS (DART-TOF) m/z calcd for $C_{13}H_{19}NO_2$ $[M + H]^+$ 222.1489, found 222.1513.

*cis-2-tert-Butyl-5-(2-pyridyl)-1,3-dioxane Hydrobromide (**17**).* A solution of 125 mg (0.56 mmol) of **15** and 387 mg (2.82 mmol) of freshly distilled *tert*-butyl bromide in 2.5 mL of dry $CHCl_3$ was heated at reflux for 12 h and then allowed to cool to room temperature.[10] Volatile components were removed by rotary evaporation to yield 165 mg (98%) of the title compound as an off-white powder. The solid was recrystallized from CH_2Cl_2/pentane to give colorless crystals: mp (dec) 178−181 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (s, 9H), 3.87−3.91 (br m, 1H), 4.22−4.40 (m, 4H), 4.27 (s, 1H), 7.87 (t, J = 6.5 Hz, 1H), 8.37 (td, J = 7.9 Hz, J = 1.2 Hz, 1H), 8.49 (d, J = 8.2 Hz, 1H), 8.70 (d, J = 5.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.7, 35.3, 36.7, 69.3, 108.7, 125.0, 128.1, 140.3, 145.4, 158.4; HRMS (DART-TOF) m/z calcd for $C_{13}H_{20}BrNO_2$ $[M - Br]^+$ 222.1489, found 222.1520.

*trans-2-tert-Butyl-5-(2-pyridyl)-1,3-dioxane Hydrobromide (**18**).* A solution of 54.3 mg (0.25 mmol) of **16** and 171.3 mg (1.25 mmol) of freshly distilled *tert*-butyl bromide in 5 mL of dry chloroform was heated at reflux for 12 h and then allowed to cool to room temperature.[10] Volatile components were removed by rotary evaporation to yield 70.4 mg (93%) of an off-white powder that was recrystallized from $CHCl_3$/Et_2O: mp (dec) 156−170 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (s, 9H), 1.78 (br s, 1H exchanges), 3.84 (tt, J = 6.0 Hz, J = 4.8 Hz, 1H), 4.24−4.40 (m, 4H), 4.41 (s, 1H), 7.78 (d, J = 8.0, 1H), 7.92 (t, J = 6.4 Hz, 1H), 8.41 (td, J = 7.9, J = 1.4, 1H),

DOI: 10.1021/acs.joc.6b02428
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8.91 (d, J = 5.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.8, 35.1, 41.1, 69.3, 107.7, 125.7, 127.0, 142.5, 146.4, 153.4; HRMS (DART-TOF) m/z calcd for $C_{13}H_{20}BrNO_2$ $[M - Br]^+$ 222.1489, found 222.1472. Rapid equilibration of **18** to **17** occurs on standing and especially in solution. For this reason, the spectroscopic data reported above for **18** were obtained from mixtures of **18** and **17**. Detailed NMR spectra are provided in the Supporting Information

Equilibrations. For each pair of anancomeric dioxanes, equilibrium was approached independently from pure samples of each isomer. The isomers were equilibrated at room temperature (~23 °C) in sealed ampules under nitrogen as solutions in cyclohexane and Et_2O 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 isomer, it was deemed that equilibrium had been attained. Area ratios for each equilibrium were taken as the average of 5−14 independent determinations from each side, the isomers were assumed to have identical GC response ratios, and the equilibrium constant for the each equilibrium (Table 1) was determined from these area ratios.

X-ray Crystallography. Structures were solved by direct methods using SHELXS and refined against F^2 on all data by full-matrix least-squares with SHELXL.[35] 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 **3** and **15** can be found in the Supporting Information. Full details of the X-ray structure determinations are available for 15 and 3. Additionally, CCDC nos. 1498697 (**3**) and 1498696 (**15**) contain the supplementary crystallographic data for this paper.[36]

Calculations. The calculations and the Hirshfeld charge calculations were carried out using Gaussian-09.[11] The structures were drawn using CYLview 1.0b.[37]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02428.

NMR spectra of all products; ^{1}H NOESY spectra and analyses; details of the X-ray crystallography; analytical GC data; a summary of the calculations, including computed energies and coordinates (PDF)

X-ray data for compound **15** (CIF)

X-ray data for compound **3** (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported in part by the facilities and staff of the Yale University Faculty of Arts and Sciences High Performance Computing Center. The work at the University of Connecticut was supported by grants from Procter & Gamble Pharmaceuticals, Mason, OH, and the Process Chemistry Division, H. Lundbeck A/S, Copenhagen, Denmark.

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