# The Role of CH⋯O Coulombic Interactions in Determining Rotameric Conformations of Phenyl Substituted 1,3-Dioxanes and Tetrahydropyrans

Kenneth B. Wiberg,*,[†] Kyle M. Lambert,[‡] and William F. Bailey*,[‡]

[†]Department of Chemistry, Yale University, New Haven, Connecticut 06520-8107, United States
[‡]Department of Chemistry, University of Connecticut, Storrs, Connecticut 06269-3060, United States

S Supporting Information

ABSTRACT: The rotameric conformations of the phenyl ring in both the axial and the equatorial conformers of phenyl substituted 1,3-dioxanes and tetrahydropyrans are compared with those of the corresponding phenylcyclohexanes at the MP2/6-311+G* level. The compounds with an axial phenyl commonly adopt a conformation in which the plane of the aromatic ring is perpendicular to the benzylic C−H bond. However, axial 5-phenyl-1,3-dioxane adopts a "parallel" conformation that allows an ortho hydrogen to be proximate to the two ring oxygens, leading to attractive CH⋯O interactions. Stabilizing Coulombic interactions of this sort are found with many of the oxygen-containing six-membered rings that were investigated.
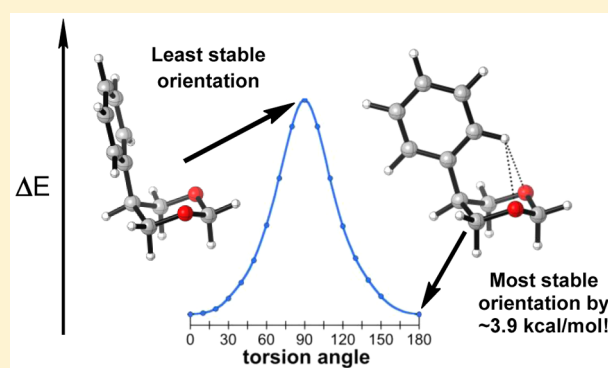
INTRODUCTION

Some time ago, Allinger and Tribble,[1] in an early application of the molecular mechanics method, demonstrated that the phenyl ring in equatorial phenylcyclohexane preferentially adopts a rotameric conformation in which the aromatic ring eclipses the benzylic C−H bond ("phenyl parallel" conformation). This arrangement avoids unfavorable steric interaction between the ortho hydrogens of phenyl and the equatorial hydrogens at C(2) and C(6) of the cyclohexane chair. In contrast, axial phenylcyclohexane adopts a "phenyl perpendicular" conformation in which the plane of the aromatic ring is orthogonal to the benzylic C−H bond (and flatside-on to the syn-axial hydrogens). Accordingly, the steric interaction in the axial phenylcyclohexane ground state is due mainly to compression of the ortho hydrogens of the phenyl ring with the equatorial cyclohexyl hydrogens at C(2) and C(6) and only partly to syn-axial repulsion. This GS repulsion leads to a relatively low rotational barrier. More recently, we reported the results of a more detailed ab initio study of phenylcyclohexane and 1-methyl-1-phenylcyclohexane that were in accord with the conclusions drawn from the MM1 analysis.[2]

It has been tacitly assumed that the rotameric arrangement of a phenyl group in saturated six-membered heterocycles corresponds, at least qualitatively, to that found in axial and equatorial phenylcyclohexane. As we show below, this is not always the case: attractive Coulombic interactions between the ortho hydrogen of a phenyl ring and an oxygen in a 1,3-dioxane or tetrahydropyran can dramatically alter the preferred rotameric conformation of the aromatic ring.[3]

RESULTS AND DISCUSSION

In an effort to investigate the potential effect of ring heteroatoms on the rotameric behavior of phenyl-substituted saturated six-membered heterocycles, we have examined phenyl-substituted 1,3-dioxanes and tetrahydropyrans and compared the results to those found for the corresponding phenylcyclohexanes. As noted above, we have reported a computational study of the latter that found that MP2 is more satisfactory than DFT.[2] Therefore, all of the compounds were studied at the MP2/6-311+G* level for the geometry optimizations, the vibrational frequencies, and the rotational barrier scans. The effect of internal rotation of the phenyl group in the systems studies leads to non-negligible contributions to the free energies of these molecules. These entropic contributions are not of much importance in the present context, and for this reason, we chose to focus on computation of ΔH rather than ΔG. The results of these studies, corrected for differences in zero-point energies and thermal corrections to 25 °C, are summarized in Table 1, and the computed structures are shown in Figure 1. Details of the calculations may be found in the Supporting Information.

As expected, the compounds with an equatorial phenyl have a lower energy than the corresponding axial substituted isomers. Most of the equatorially substituted compounds (**1**, **3**, **5**, **9**, and **11**) display a similar preferred rotameric arrangement of the phenyl group, adopting a "parallel" conformation (τ, H−C−C≡C, ~0°), whereas equatorial 2-

Table 1. MP2/6-311+G* Ground-State Conformational Enthalpies, Torsional Angles, and Dipole Moments

compound	τ^a	μ (D)	$\Delta H°$ (298 K)^b
ax-phenylcyclohexane (**2**)	66.5	0.451	3.24
eq-phenylcyclohexane (**1**)	0.0	0.530	0.00
ax-2-phenyl-1,3-dioxane (**4**)	87.5	2.460	1.13
eq-2-phenyl-1,3-dioxane (**3**)	0.0	2.457	0.00
ax-5-phenyl-1,3-dioxane (**6**)	0.0	2.303	0.83
eq-5-phenyl-1,3-dioxane (**5**)	0.0	2.483	0.00
ax-2-phenylTHP (**8**)	100.3	1.584	2.19
eq-2-phenylTHP (**7**)	27.9	1.877	0.00
ax-3-phenylTHP (**10**)	143.3	1.774	0.72
eq-3-phenylTHP (**9**)	3.7	1.667	0.00
ax-4-phenylTHP (**12**)	60.7	1.626	3.53
eq-4-phenylTHP (**11**)	0.0	1.504	0.00

^{a}H−C−C=C ground-state torsion angle. τ = 0° corresponds to the phenyl parallel conformation; τ = 90° corresponds to the phenyl perpendicular conformation. ^{b}kcal/mol.

phenyltetrahydropyran (**7**) has τ = 27.9°. The twisted conformation adopted by **7** places an ortho-hydrogen of the phenyl in rather close proximity to the ring oxygen of the THP;

this aspect is discussed in further detail below. The conformations of the equatorially substituted compounds (other than **7**) have the benzylic C−H bond eclipsed with the aryl ring. This is largely the result of steric interactions between the ortho-hydrogens of the phenyl group and the equatorial hydrogens of the ring to which it is attached, as noted by Allinger and Tribble.[1] While most of the equatorially phenyl-substituted molecules have similar structures, there are significant differences in rotational barriers.

The rotational barriers are of importance to achieving an understanding of the differences in rotameric conformational preferences, particularly for the axially substituted six-membered rings. The barriers have been studied by carrying out geometry optimizations with the torsion angle between the aryl ring and the benzylic C−H bond stepped at 10° intervals. The rotational profiles, which are shown in Figure 2, do not include the effect of differences in zero-point energies. The maxima in each of the rotational profiles were further characterized by geometry optimizations for the higher energy rotamers, displayed in Figure 2, to transition states, followed by vibrational frequency calculations and corrections for zero-point energies and thermal energies. These data are summarized in Table 2; the $\Delta E^{\ddagger}$ at 0 K (which = $\Delta H^{\ddagger}$ at 0
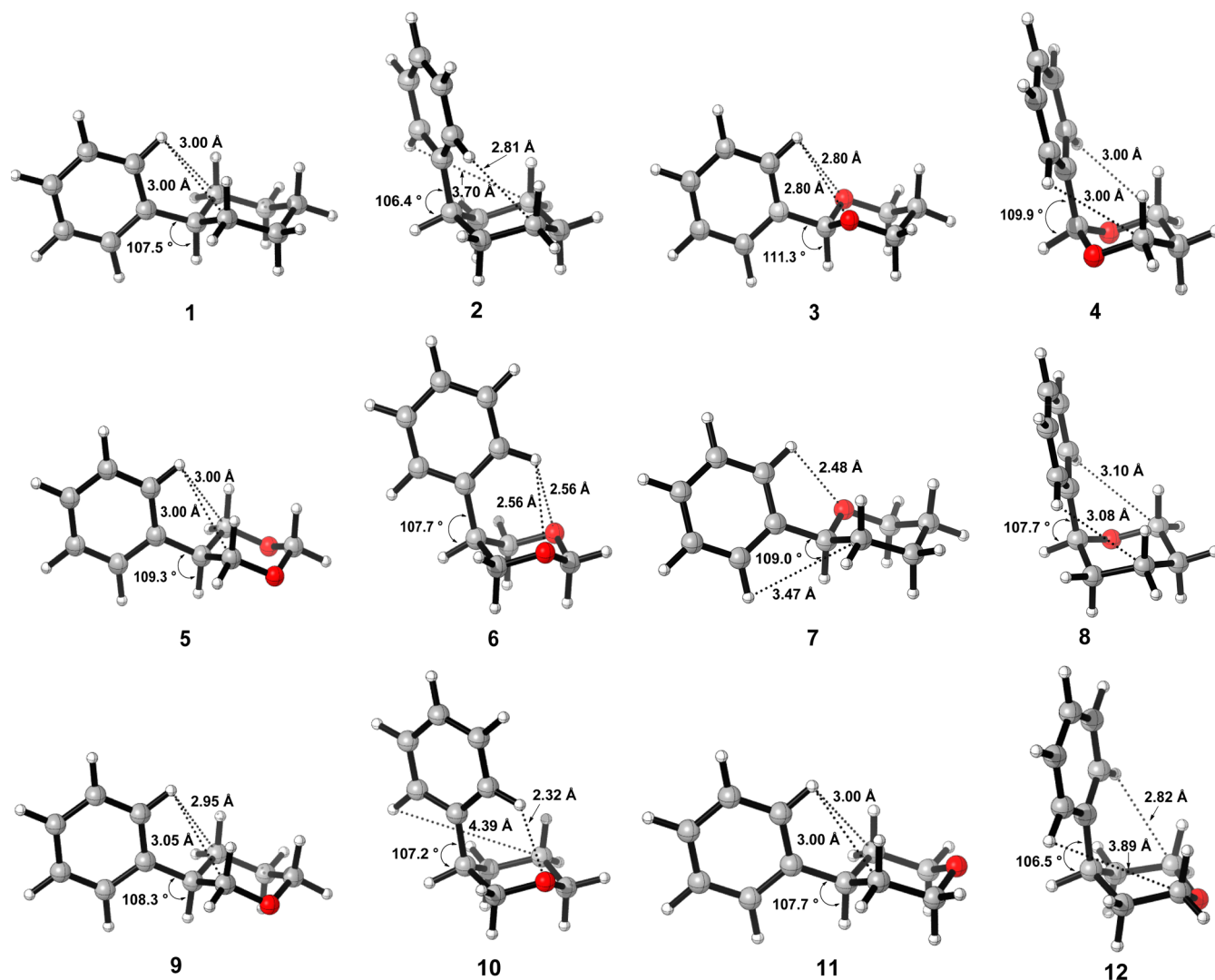
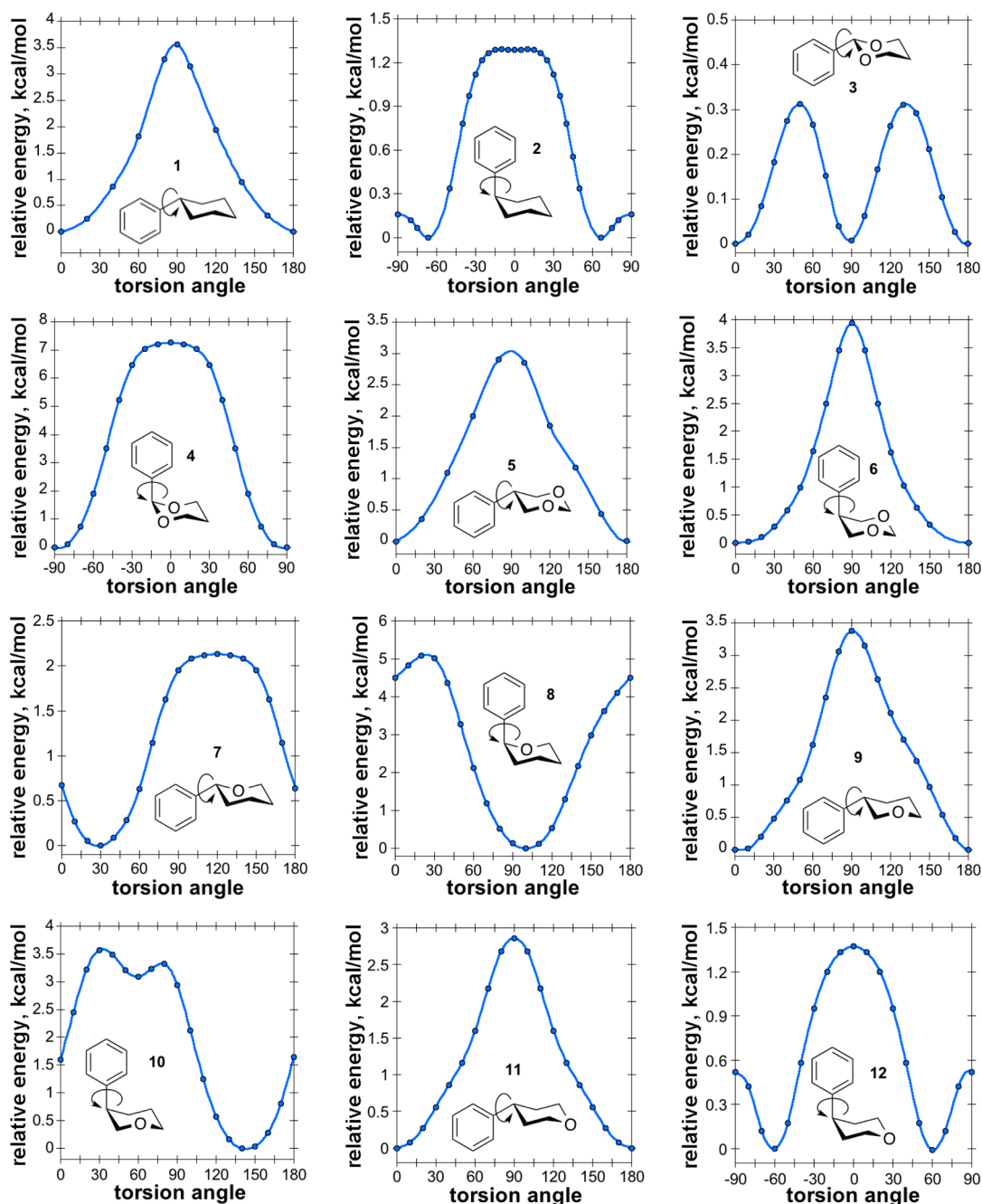**Figure 1.** MP2/6-311+G* optimized ground-state structures.

Figure 2. Rotational profiles.

K) are given along with $\Delta H^{\ddagger}$ at 298 K (25 °C). The relatively large thermal corrections are mainly due to a loss of a vibrational mode on going from the ground state to the transition state. The computed transition-state structures are displayed in Figure 3. Now, all of the readily obtained information is in hand for studying the conformational preferences.

The barriers to phenyl rotation in the equatorial phenyl compounds **1**, **5**, **7**, **9**, and **11** are similar and largely the result of steric interactions between the ortho-hydrogens of the phenyl group and the equatorial hydrogens of the ring to which it is attached. However, equatorial 2-phenyl-1,3-dioxane (**3**) is strikingly different than the other equatorially substituted compounds. The phenyl−C(2) rotational barrier in **3** is only 0.3 kcal/mol with approximately equal energetic minima at τ =

0 and 90° (Figure 2). The barrier is reduced even more at 298 K because of the difference in thermal correction for the GS and TS. Indeed, an experimental study found this compound to have a very small barrier; the phenyl is virtually a free-rotor.[4] This low barrier must be related to the dioxane oxygens since this is the only source of a difference with respect to the other compounds. In **3**, the destabilizing ortho-hydrogen/equatorial hydrogen interactions that beset the phenyl "perpendicular" conformers in **1**, **5**, **9**, and **11** are replaced by far less severe ortho-hydrogen/oxygen interactions. In addition, the ortho-hydrogens are at small distances from the oxygens at 90°, and as described below, this leads to an attractive CH⋯O Coulombic attraction.[5]

The equatorially substituted 2-phenyltetrahydropyran (**7**), with a rotational barrier of 2.3 kcal/mol (Table 2), presents a

Table 2. MP2/6-311+G* Transition-State Energies, Torsional Angles, and Dipole Moments

compound	τ^a	μ (D)	$\Delta E^{\ddagger}$ (0 K)^b	$\Delta H^{\ddagger}$ (298 K)^b
ax-phenylcyclohexane (**2**)	10.0	0.437	1.12	0.68
eq-phenylcyclohexane (**1**)	90.0	0.649	3.73	3.14
ax-2-phenyl-1,3-dioxane (**4**)	0.0	2.331	6.65	6.29
eq-2-phenyl-1,3-dioxane (**3**)	49.5	2.609	0.33	−0.26
ax-5-phenyl-1,3-dioxane (**6**)	90.0	2.315	4.12	3.46
eq-5-phenyl-1,3-dioxane (**5**)	90.0	2.402	3.28	2.68
ax-2-phenylTHP (**8**)	24.2	1.793	4.67	4.33
eq-2-phenylTHP (**7**)	134.6	1.793	2.26	1.67
ax-3-phenylTHP (**10**)	39.0	1.832	3.50	3.01
eq-3-phenylTHP (**9**)	90.0	1.614	3.54	2.96
ax-4-phenylTHP (**12**)	0.0	1.566	1.30	0.85
eq-4-phenylTHP (**11**)	90.0	1.494	3.03	2.43

^{a}H−C−C═C ground-state torsion angle. $\tau = 0°$ corresponds to the phenyl parallel conformation; $\tau = 90°$ corresponds to the phenyl perpendicular conformation. ^{b}kcal/mol.
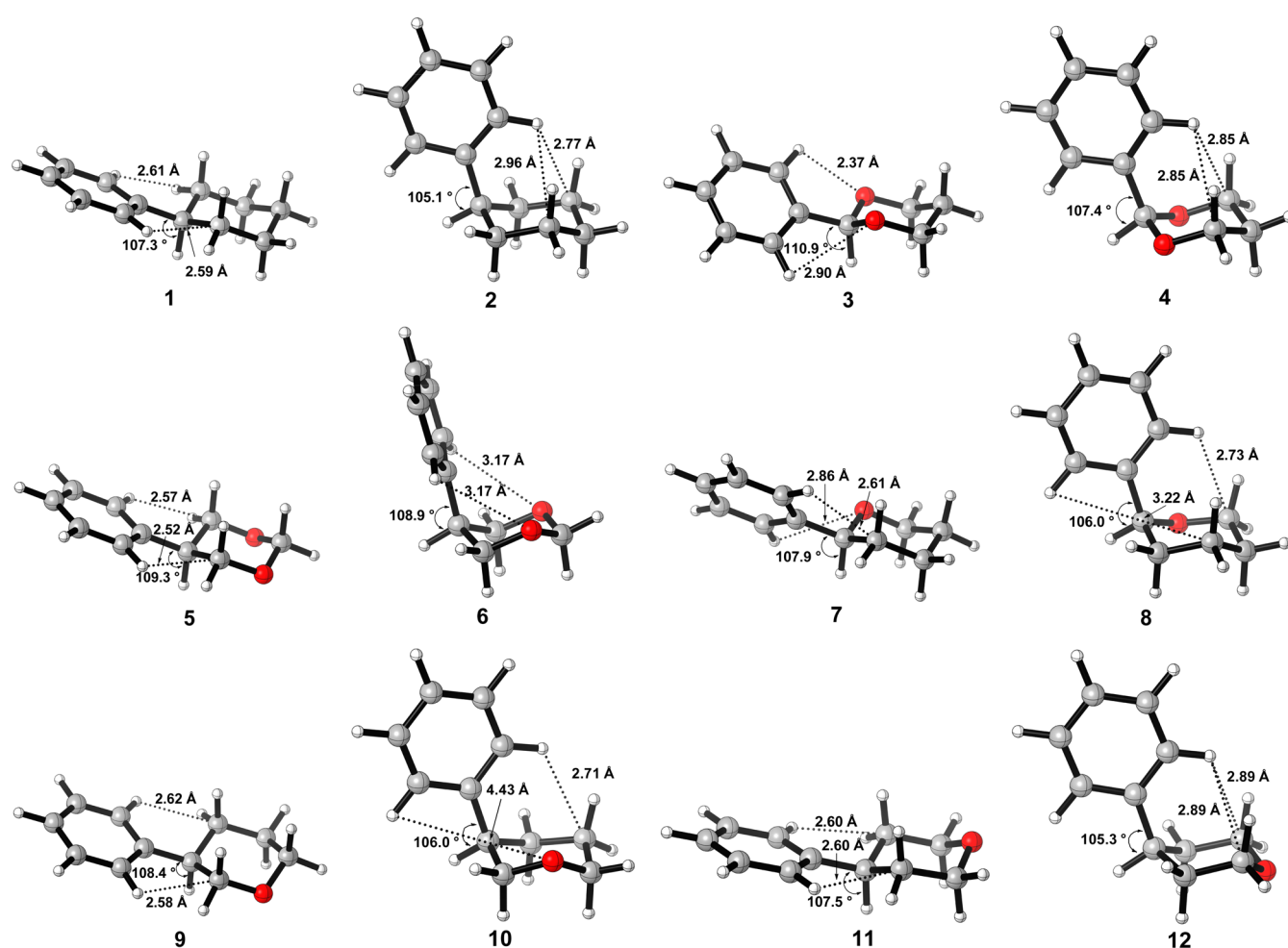

Figure 3. MP2/6-311+G* transition-state structures.

somewhat different situation than the compounds discussed above. The ground-state structure of **7** (Figure 1 and Table 2) displays a torsion angle that is increased from the phenyl parallel arrangement to 27.9°. As noted above, this involves twisting of the phenyl ring to bring an ortho hydrogen rather close to the THP oxygen. This behavior is most easily rationalized as resulting from an attractive CH···O Coulombic interaction. One way to test this hypothesis is to examine the charges at the atoms involved in the interaction between the

nearby ortho-hydrogen and the ring oxygen. To this end, the Hirshfeld charges, derived from the electron density distribution, were computed;[6] the details may be found in the Supporting Information. It was found that the ortho aryl hydrogen in **7** has a charge of +0.046e, and the oxygen has a charge of −0.225e. The hydrogen charge is quite reasonable: it has been found experimentally that there is very little charge separation in the C−H bonds of methane,[7] and the increased s-character of the phenyl C−H bonds should lead to a small

positive charge on the hydrogens. On this basis, a rough estimate of the Coulombic energy ($E = q_1 q_2 / r$) associated with the CH···O interaction in **7** at a distance of 2.49 Å is 1.4 kcal/mol.[8] Clearly, an attractive interaction of this magnitude could easily lead to the observed torsion angle. Other factors may also be important in determining the net interaction, and this simple calculation is presented to help make the CH···O attraction plausible.

The rotameric arrangements of the compounds bearing an axial phenyl are potentially more interesting than those of the equatorially substituted analogues. A comparison of axial 2-phenyl-1,3-dioxane (**4**) with axial phenylcyclohexane (**2**) finds (Table 2) that, whereas **2** has a relatively small rotational barrier ($\Delta E^{\ddagger} = 1.1$ kcal/mol), **4** has an unusually large barrier of 7.1 kcal/mol. The barrier to rotation of the axial phenyl group in **2** is reduced because there is some repulsion between the ortho hydrogens of the phenyl ring and equatorial C(2) hydrogens of the cyclohexane, leading to ground-state destabilization of **2**. Conversely, in axial 2-phenyl-1,3-dioxane (**4**), the equatorial C(2) hydrogens present in **2** are replaced with oxygen atoms. Thus, the steric interaction between the ortho hydrogens and the equatorial C(2) hydrogens that plague **2** are absent in the dioxane analogue. Moreover, the ortho-hydrogens of the axial phenyl ring in **4** are close to the dioxane oxygens, and this presumably leads to a CH···O attraction. Consequently, in the case of axial 2-phenyl-1,3-dioxane (**4**), the ground state is stabilized, leading to the large barrier to rotation.

The most fascinating of the axially phenyl-substituted compounds are axial 5-phenyl-1,3-dioxane (**6**) and axial 3-phenyltetrahydropyran (**10**). The first of these compounds (**6**) adopts a perfectly parallel conformation (Table 1) in which the plane of the phenyl ring bisects the 1,3-dioxane ring. To our knowledge, this is the only example of a six-membered saturated ring bearing an axial aryl group in which the aryl ring adopts such a ground-state conformation. Indeed, a previous analysis of the conformational behavior of axial 5-phenyl-1,3-dioxane had tacitly assumed that the phenyl would adopt the perpendicular arrangement found in axial phenyl-cyclohexane.[9] It is difficult to envision any interaction that might uniquely favor the phenyl parallel conformation in **6** other than an attractive Coulombic interaction between an ortho-hydrogen of the phenyl ring and the 1,3-oxygens of the dioxane at the computed distance of 2.56 Å. This hypothesis was tested computationally by replacing the phenyl group in axial 5-phenyl-1,3-dioxane (**6**) with a 2-pyridyl ring. In axial 5-pyridyl-1,3-dioxane, the nitrogen atom will bear a negative charge, leading to a repulsive interaction with the negatively charged oxygens of the 1,3-dioxane in the parallel rotamer having the nitrogen neighboring the oxygens. As shown in Figure 4, axial 5-pyridyl-1,3-dioxane adopts an approximately perpendicular conformation with the pyridyl ring twisted (τ, N=C−C−H, ∼30°) from a perfectly perpendicular conformation to position the nitrogen close to one of the equatorial hydrogens at C(4) of the dioxane. The maximum energy rotamer is found when the nitrogen of the pyridyl ring is between the two oxygens of the 1,3-dioxane (τ, N=C−C−H, = 180°). In the absence of the nitrogen, the energy at $\tau = 180°$ would be close to zero. The calculated barrier of 4.5 kcal/mol is apparently the result of a N···O repulsive interaction. The nitrogen-to-oxygen distance in the least stable conformation of axial 5-pyridyl-1,3-dioxane is 3.21 Å, and the O and N Hirshfeld charges are −0.182e and −0.198e, respectively. Consequently,
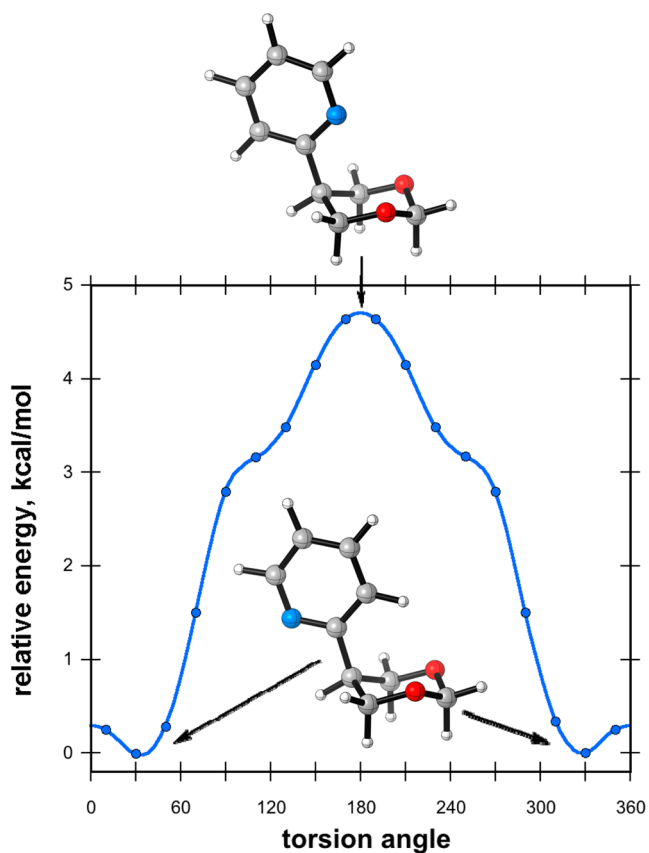

Figure 4. Rotational profile for ax-5-(2-pyridyl)-1,3-dioxane.

there is a repulsive Coulombic energy of ∼3.7 kcal/mol per N···O pair or a total of about 7.4 kcal/mol for the maximum energy rotamer having the nitrogen of the pyridyl ring between the two oxygens of the 1,3-dioxane. Considering the approximations in this simple approach, the result is in reasonable agreement with the 4.5 kcal/mol computed rotational barrier.[10]

An attractive CH···O interaction is also found in the conformation adopted by axial-3-phenyltetrahydropyran (**10**). The phenyl ring in **10** is rotated 39° from the phenyl perpendicular conformation (Table 1) so as to place an ortho-hydrogen of the phenyl ring near the oxygen of the THP. An estimate of the attractive interaction between the proximate ortho-phenyl hydrogen in **10** and the oxygen of the THP ring is easily obtained from the Hirshfeld charges on the ortho-hydrogen (+0.038e) and the oxygen (−0.175e) at the computed distance between the hydrogen and the oxygen of 2.32 Å; the Coulombic interaction is attractive by ∼1.0 kcal/mol. There are of course many other interactions present in these axially substituted compounds, but it appears that an attractive CH···O interaction has a major effect on the rotameric ground-state arrangement of a phenyl group in heteroatom-containing six-membered rings. In short, when possible, an ortho-hydrogen in a phenyl ring positions itself to be close to an oxygen atom in the ring to which it is attached.

■ CONCLUSIONS

The phenyl-substituted tetrahydropyrans and 1,3-dioxanes have proven to be very useful in examining weak interactions between C−H and O. Such interactions have been noted previously,[5] but as far as we can determine, we have observed the first cases in which aryl rings rotate so as to place an aryl

hydrogen close to an oxygen. The extra s-character in an aryl C−H bond, vis-à-vis an aliphatic C−H bond, increases the positive charge at the hydrogen, leading to a larger attractive Coulombic attraction for a ring oxygen.

CALCULATIONS

The ab initio calculation and population calculations were carried out using Gaussian 09.[11] The structures were drawn using CYLview 1.0b.[12]

ASSOCIATED CONTENT

Ⓢ Supporting Information

Tables of computed energies and coordinates, information on calculated atomic charges. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01340.

AUTHOR INFORMATION

Corresponding Authors
*E-mail: Kenneth.Wiberg@yale.edu (K.B.W.).
*E-mail: William.Bailey@uconn.edu (W.F.B.).

Notes
The authors declare no competing financial interest.

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