Energetics of Oxaspirocycle Prototypes: 1,7-Dioxaspiro[5.5]undecane and 1,7,9-Trioxadispiro[5.1.5.3]hexadecane
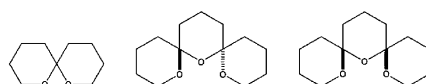
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1,7-Dioxaspiro[5.5]undecane, *trans*- and *cis*-1,7,9-Trioxadispiro[5.1.5.3]hexadecane

The relative gas-phase energetics of several low-lying isomers of 1,7-dioxaspiro[5.5]undecane and 1,7,9-trioxadispiro[5.1.5.3]hexadecane have been calculated with second-order Møller–Plesset perturbation theory and basis sets as large as aug-cc-pVQZ. Relative energies in THF, dichloromethane, acetone, and DMSO have been estimated with corrections from polarized continuum model calculations at the B3LYP/6-311+G(d) level. In the most stable conformation of 1,7-dioxaspiro[5.5]undecane, both rings adopt chair conformations, and both oxygens are axially disposed (**2A**). It is more than 2 kcal mol^{-1} more stable than all the other conformers. In agreement with previous work, the "twist-boat" trans isomer (**3A**) is the most stable isomer of 1,7,9-trioxadispiro[5.1.5.3]hexadecane. However, in contrast to this earlier study, an "all-chair" conformation (**3B**) is found to be the most stable cis isomer of 1,7,9-trioxadispiro[5.1.5.3]hexadecane ($\Delta E \approx 0.5$ kcal mol^{-1} in acetone and DMSO). Gauge-independent atomic orbital computations at the B3LYP/6-311+G(d) level indicate that this is the only cis isomer with ^{13}C NMR chemical shifts that are qualitatively consistent with the experimental spectra.

1. Introduction

Oxaspirocycles are common substructures in many important naturally occurring biologically active products.[1–4] Oxaspirocyclic motifs can be found in antibiotics, insect pheromones, and toxins and, more recently, have garnered much attention because of their presence in marine toxins such as azaspiracid.[1,3,5] Reference 3 provides an excellent review of bis-spiroacetal ring systems (also known as bis-spiroketals) through 1999.

These systems have very diverse potential energy surfaces. For example, in the simple oxaspirocycles shown in Figure 1, each six-membered ring can adopt a chair, boat, or twist-boat
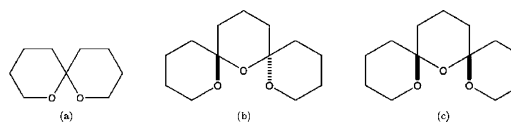

FIGURE 1. Oxaspirocycle prototypes used in this study: (a) 1,7-dioxaspiro[5.5]undecane, (b) *trans*-1,7,9-trioxadispiro[5.1.5.3]hexadecane, and (c) *cis*-1,7,9-trioxadispiro[5.1.5.3]hexadecane.

conformation. However, the anomeric effect can significantly stabilize the boat and twist-boat conformations, thereby giving rise to several energetically competitive minima. In addition, some trioxadispirocyclic systems can interconvert between cis and trans isomers under certain conditions. Despite this qualitative understanding of the energetics, relatively little quantitative data are available for these important oxaspirocyclic systems. One goal of this work is to compute quantitatively reliable relative energies for the conformers of the simple prototypes shown in Figure 1.

In 1981, Deslongchamps et al. were able to infer the conformational energetics of 1,7-dioxaspiro[5.5]undecanes by using energetic parameters of the gauche forms of butane and

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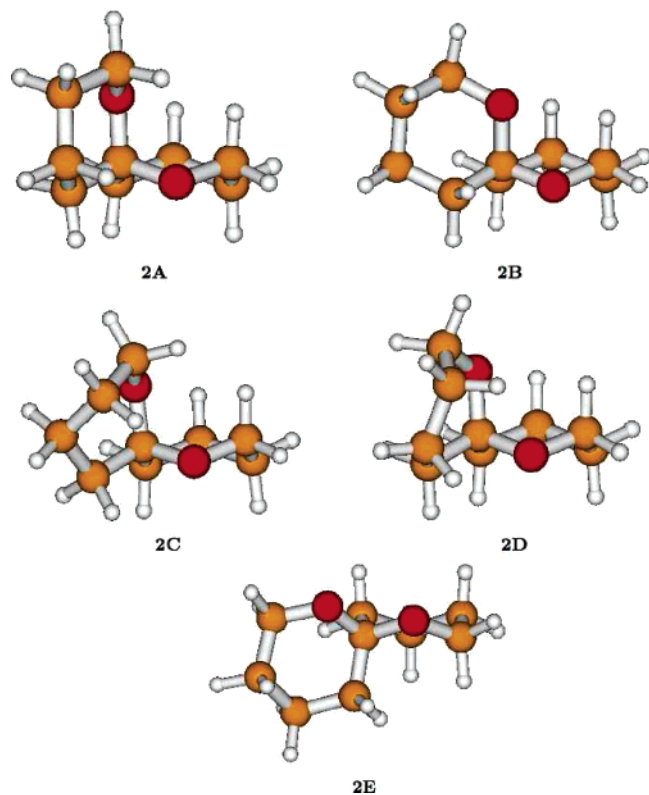
FIGURE 2. Low-energy conformers of 1,7-dioxaspiro[5.5]undecane.

n-propylether obtained from equilibrium studies. These energetic contributions were then combined with an accepted value for the anomeric effect to produce an energetic model for the various conformations of these bicyclic systems.[6] According to this widely cited study, the most stable conformer of 1,7-dioxaspiro-[5.5]undecane (i.e., the global minimum) is structure **2A** shown in Figure 2. In this conformer, both rings adopt a chair conformation, and both oxygens are in the axial position (with respect to the neighboring ring).[7] This analysis also predicts that structures **2B,E** lie 2.4 kcal mol^{-1} and 4.8 kcal mol^{-1}, respectively, above **2A**. Like **2A**, the rings in **2B,E** adopt chair conformations. In **2B**, however, only one oxygen is in the axial position while neither oxygen is axial in **2E** (i.e., both are equatorial). Experimentally, only a single conformer, **2A**, is observed.[6]

NMR studies by McGarvey et al. in 1996 were used to rationalize the relative energetics of 1,7,9-trioxadispiro[5.1.5.3]-hexadecane isomers. Equilibrium studies were performed to determine the relative stability of the cis and trans isomers (Figure 1) in a range of solvents. For both the cis and the trans isomers, the peaks observed in the ^{13}C NMR spectra were assigned to a conformation in which the central ring adopts a twist-boat conformation while both side rings adopt chair conformations, placing all three oxygen atoms in an axial or pseudoaxial position with respect to the neighboring ring(s). These cis and trans isomers correspond to **3E,A** in Figure 3.The trans isomer predominated in all solvents, but this preference

was attenuated in polar solvents.[8,9] For example, **3A** was found to be 0.7 kcal mol^{-1} more stable than **3E** in hexane and 0.3 kcal mol^{-1} more stable than **3E** in DMSO.

With only exiguous energetic data available for these important systems, we have carried out a series of electronic structure computations designed to help fill this conspicuous void by probing the relative energetics of the most stable conformations of 1,7-dioxaspiro[5.5]undecane and 1,7,9-trioxadispiro[5.1.5.3]hexadecane. This work presents the first detailed energetic analysis of the most stable isomers of these important systems in the gas phase and in four common solvents (THF, dichloromethane (DCM), acetone, and DMSO).

2. Computational Details

More than 30 minima of 1,7-dioxaspiro[5.5]undecane and 58 minima of 1,7,9-trioxadispiro[5.1.5.3]hexadecane have been identified by considering structures previously reported in the literature along with those from high temperature molecular dynamics simulations. With the exception of **2E**, only isomers within 6 kcal mol^{-1} of the global minimum in the gas phase are presented in this work (see section 3).

After testing several methods and basis sets, it was observed that the relative energies of 1,7-dioxaspiro[5.5]undecane are rather insensitive to the geometry optimization procedure (see Supporting Information). Consequently, all isomers have been optimized with the B3LYP[10,11] density functional and the 6-311+G-(*d*) split valence triple-ζ basis set. Conformers **2A,E** and **3A** were constrained to C_2 symmetry while **3B** was constrained to C_s symmetry. No symmetry constraints were employed on the remaining isomers. Harmonic vibrational frequencies were computed with analytic second derivatives to ensure that each isomer corresponds to a minimum on the potential energy surface and to obtain zero-point vibrational energy (ZPVE) corrections to the relative energies.

Recently, it was shown that the B3LYP density functional method does not reliably describe the conformational energetics of some simple cyclohexane and tetrahydropyran compounds.[12] Consequently, a series of second-order Møller−Plesset perturbation theory (MP2)[13] single-point energy computations were performed on the optimized structures with a family of correlation consistent basis sets (aug-cc-pVXZ for O and cc-pVXZ for H and C, where X = D, T, Q).[14,15] These basis sets are denoted as aDZ, aTZ, and aQZ. The gas-phase relative energies (ΔE_{gas}) reported in this work were determined by comparing the MP2 electronic energies of the various conformers to the global minimum.

Solvent effects were estimated at the B3LYP/6-311+G(*d*) level with the integral equation formalism polarized continuum model (IEFPCM) of the self-consistent reaction field method.[16] Dielectric constants of $\epsilon = 7.58$ for THF, $\epsilon = 8.93$ for DCM, $\epsilon = 20.7$ for acetone, and $\epsilon = 46.7$ for DMSO were used in the IEFPCM calculations to predict the influence of these solvents on the energetics of the low-energy isomers of 1,7-dioxaspiro[5.5]undecane and 1,7,9-trioxadispiro[5.1.5.3]hexadecane. The structure of each isomer was re-optimized in all four solvents. The relative energies

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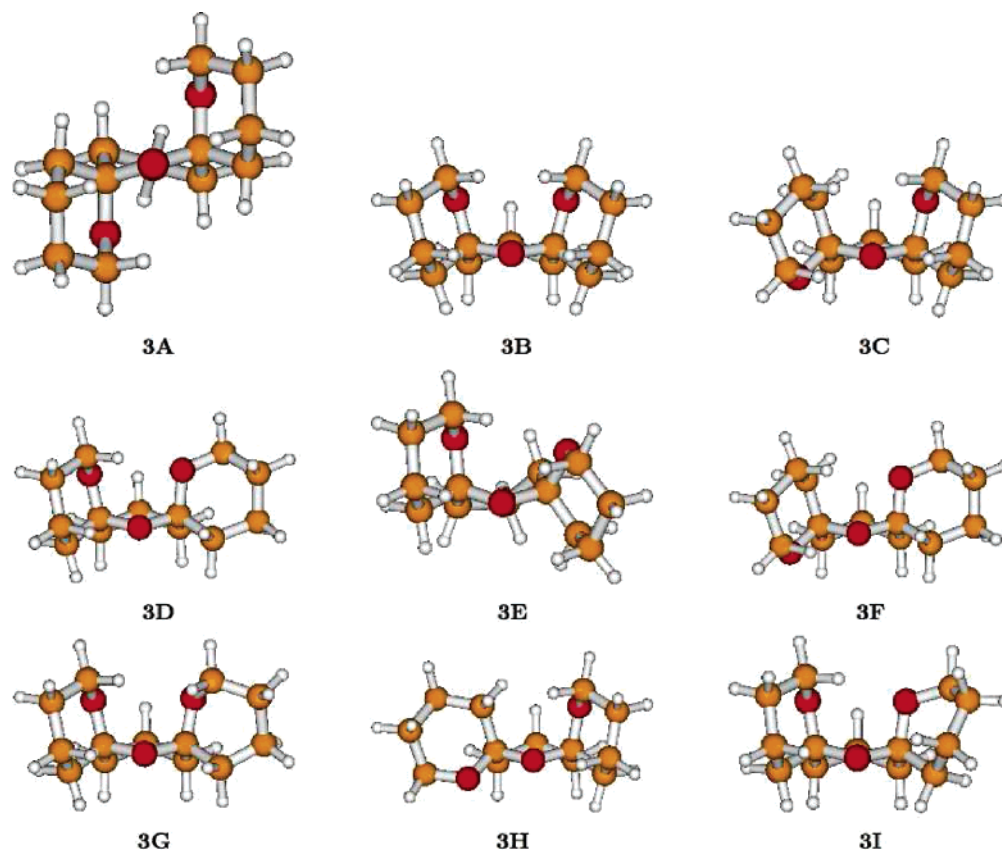
FIGURE 3. Low-energy conformers of *cis*- and *trans*-1,7,9-trioxadispiro[5.1.5.3]hexadecane.

in each solvent were then compared to the B3LYP/6-311+G(*d*) ΔE_{gas} to obtain a solvation correction (δE_{solv}) for each isomer in each solvent. These corrections (see Supporting Information) were then combined with the MP2 ΔE_{gas} to estimate the relative energies in each solvent (ΔE_{solv} where solv = THF, DCM, acetone, or DMSO).

$$\Delta E_{solv} = \Delta E_{gas} + \delta E_{solv} \qquad (1)$$

^{13}C NMR chemical shifts were calculated with the gauge-independent atomic orbital (GIAO) method[17] for the five lowest energy isomers of 1,7,9-trioxadispiro[5.1.5.3]hexadecane. The GIAO computations were performed both in the gas phase (using B3LYP/6-311+G(*d*) structures and densities) as well as in chloroform and DMSO (using PCM-B3LYP/6-311+G(*d*) structures and densities). The ^{13}C NMR chemical shifts were computed relative to those calculated for TMS in the gas phase (184.17 ppm), in

chloroform (184.50 ppm), and in DMSO (184.73 ppm). These values are reported in Supporting Information.

All calculations used spherical harmonic 5*d*, 7*f*, and 9*g* functions rather than their 6*d*, 10*f*, and 15*g* Cartesian counterparts. Electronic energies were converged to at least 1×10^{-6} E$_h$, and Cartesian gradients were converged to 2×10^{-5} E$_h$ bohr^{-1}. The Gaussian 03 program package was used to perform all B3LYP and IEFPCM computations[18] while all MP2 energies were computed with MPQC.[19-23]

3. Results and Discussion

3.1. 1,7-Dioxaspiro[5.5]undecane. In the dioxaspirocyclic system, four low energy conformers were identified and are shown in Figure 2 along with structure **2E** from the study of Deslongchamps and co-workers.[6] Conformers **2A,B,E** have already been described in section 1. Like **2A**, **2C,D** have both oxygens in the axial position with respect to the neighboring ring. However, one of the rings adopts a boat conformation in **2C** and a twist-boat conformation in **2D**.

Table 1 provides the relative energies for **2A**−**E** in the gas phase as well as in four different solvents. Also included are

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TABLE 1. Relative Electronic Energies (ΔE in kcal mol^{-1}) and Dipole Moments (μ_{gas} in debye) of 1,7-Dioxaspiro[5.5]undecane in the Gas Phase and in Several Solvents

conformer	ΔE_{gas}[a]	ΔE_{THF}[b]	ΔE_{DCM}[b]	$\Delta E_{acetone}$[b]	ΔE_{DMSO}[b]	μ_{gas}[c]
2A	0.00	0.00	0.00	0.00	0.00	0.01
2B	3.86	2.92	2.93	2.70	2.62	1.91
2C	5.09	5.10	5.12	5.12	5.12	0.04
2D	5.55	5.76	5.66	5.74	5.81	0.49
2E	8.09	5.35	5.16	4.76	4.52	2.89

[a] MP2/aQZ//B3LYP/6-311+G(*d*). [b] Using solvation correction from PCM-B3LYP/6-311+G(*d*) calculations. See text for details. [c] B3LYP/6-311+G(*d*)

TABLE 2. Relative Electronic Energies (ΔE in kcal mol^{-1}) and Dipole Moments (μ_{gas} in debye) of 1,7,9-Trioxadispiro[5.1.5.3] hexadecane in the Gas Phase and in Several Solvents

isomer	ΔE_{gas}[a]	ΔE_{THF}[b]	ΔE_{DCM}[b]	$\Delta E_{acetone}$[b]	ΔE_{DMSO}[b]	μ_{gas}[c]
3A	0.00	0.00	0.00	0.00	0.00	1.36
3B	1.45	0.74	0.61	0.53	0.48	1.45
3C	1.54	0.76	0.63	0.57	0.52	1.28
3D	2.12	1.87	1.76	1.77	1.79	1.58
3E	2.21	1.79	1.73	1.65	1.65	1.42
3F	3.66	3.05	2.92	2.92	2.90	2.28
3G	3.96	3.20	3.11	2.99	2.92	1.45
3H	4.66	2.37	2.20	1.71	1.71	1.30
3I	5.16	4.80	4.68	4.65	4.67	1.54

[a] MP2/aTZ//B3LYP/6-311+G(*d*). [b] Using solvation correction from PCM-B3LYP/6-311+G(*d*) calculations. See text for details. [c] B3LYP/6-311+G(*d*)

the gas-phase dipole moments for each conformer. ΔE_{gas} represents the gas-phase relative energy from MP2/aQZ computations. This value is combined with PCM-B3LYP/6-311+G(*d*) solvent corrections in order to estimate the relative energies in each solvent (ΔE_{solv}). The solvent corrections, δE_{solv}, are described in section 2 and tabulated in Supporting Information. Note that it is imperative to re-optimize each structure in solvent. Only after re-optimizing with the IEFPCM method does ΔE_{solv} differ appreciably from ΔE_{gas}.

In agreement with previous studies,[6,7] **2A** is the most stable conformer followed by **2B**. This result holds true not only in the gas phase where **2B** lies 3.86 kcal mol^{-1} above **2A** but also in the solvents used here where ΔE ranges from 2.62 to 2.93 kcal mol^{-1}. To facilitate a comparison with the experiment, ZPVE corrections to the relative energies have been tabulated in Supporting Information. Applying this correction to **2B** decreases ΔE by 0.12 kcal mol^{-1} which yields values in each solvent that are just slightly larger than the relative energy of 2.4 kcal mol^{-1} from the model in ref 6. This model also predicts a value of $\Delta E = 4.8$ kcal mol^{-1} for conformer **2E**. However, this work has identified two new conformers (**2C,D**) that are energetically competitive with conformer **2E**. In the gas phase, **2E** lies 8.09 kcal mol^{-1} above the global minimum while **2C,D** actually have substantially smaller relative energies of 5.09 and 5.55 kcal mol^{-1}, respectively. In polar solvents, **2E** is dramatically stabilized (by as much as 3.57 kcal mol^{-1} in DMSO) and becomes energetically competitive with **2C,D**. Again, the ZPVE correction slightly stabilizes **2C,D** (by 0.10 and 0.20 kcal mol^{-1}, respectively), but it destabilizes **2E** by nearly 0.8 kcal mol^{-1}. Consequently, **2C** is more stable than **2D,E** regardless of the environment. **2D,E** have very similar energies, but **2D** is slightly more stable in the gas phase and the less polar solvents.

The data in Table 1 clearly indicate that oxaspirocyclic isomers with large dipole moments are not inherently unstable. For example, conformer **2B** has a dipole moment of 1.91 D. Yet it is always 1–3 kcal mol^{-1} more stable than **2C** or **2D** which have dipole moments of 0.04 and 0.49 D, respectively. There is, however, a connection between the dipole moment of a conformer and the magnitude of the solvation correction associated with the polar solvents examined in this study. For this particular prototype, it is fairly easy to detect the trend because the dipole moments of the conformers are well separated and the dipole moment of the global minimum is essentially zero. These solvents have essentially no effect on the relative energy of **2C** ($\mu = 0.04$ D), while they slightly destabilize **2D** ($\mu = 0.49$ D) by roughly 0.2 kcal mol^{-1}. The solvation corrections grow much larger for **2B,E**. **2B** has a dipole moment of 1.91 D and is stabilized by approximately 1 kcal mol^{-1} in these polar solvents. With the largest dipole

moment ($\mu = 2.89$ D), **2E** experiences the greatest solvation effect; it is stabilized by roughly 3 kcal mol^{-1} in the solvents examined here. Having thoroughly characterized the conformational energetics of and solvent effects in this bicyclic oxaspirocycle, we can now turn our attention to the more complicated tricyclic prototype.

3.2. 1,7,9-Trioxadispiro[5.1.5.3]hexadecane. Nine low-energy isomers of 1,7,9-trioxadispiro[5.1.5.3]hexadecane have been identified and are shown in Figure 3. Both terminal rings adopt a chair conformation in every case, aside from **3G,I** where one of the terminal rings adopts a boat conformation. Similarly, the central ring tends to be a chair except for **3A,E** in which it adopts a twist-boat conformation. The remaining distinction between isomers **3A–I** is the orientation (axial vs equatorial) of the oxygen atoms relative to the adjacent ring(s). The oxygen in the central ring tends to lie in the axial position with respect to the adjacent terminal ring. However, only one of the oxygens is axially oriented in structures **3D,F,I**. The oxygens in the terminal rings are usually in the axial position with respect to the central ring with the exception of **3C,F,H**.

Table 2 contains the relative energetics of these nine isomers. The ΔE_{gas} were obtained from MP2/aTZ electronic energies since MP2 computations with the aQZ basis set were not feasible for this larger system. Fortunately, the MP2/aTZ relative energies of 1,7-dioxaspiro[5.5]undecane were quite similar to the MP2/aQZ values. (The former is consistently 1–4% larger than the latter.) The relative energies in each solvent reported in Table 2 were obtained in the same manner as those in Table 1.

Having identified nine viable conformations of 1,7,9-trioxadispiro[5.1.5.3]hexadecane, we ranked them **3A–I** in order of relative gas-phase energy. In accord with the experimental results of McGarvey et al.,[8] the trans isomer **3A** is the most stable isomer in the gas phase as well as in all four solvents chosen. Two isomers, **3B,C**, are found to be slightly higher in energy to varying degrees depending on environment, but they are isoenergetic regardless. They lie roughly 1.7 kcal mol^{-1} above the global minimum in the gas phase but only 0.5 kcal mol^{-1} above in polar solvents. A second set of isoenergetic conformers, **3D,E**, have been identified. They are roughly 2 kcal mol^{-1} higher than **3A** in the gas phase and are stabilized by only a few tenths of a kcal mol^{-1} in the polar solvents selected. **3E** is of specific interest because it is the cis isomer described by McGarvey and co-workers.[8] The remaining isomers identified, **3F–I**, have quite large relative energies in the gas phase (3.66–5.16 kcal mol^{-1}). All four experience the expected stabilization in polar solvents, except **3H**, whose energy is

dramatically reduced from 4.66 kcal mol⁻¹ in the gas phase to 1.71 kcal mol⁻¹ in DMSO, which is a value similar to that of **3D,E**. As with the bicyclic system, ZPVE corrections tend to have very little effect on the relative energetics of **3A−I** (Supporting Information). For example, **3B** is stabilized by 0.05 kcal mol⁻¹ while **3C,D,E** are destabilized by 0.03, 0.05, and 0.11 kcal mol⁻¹, respectively. The magnitude of the ZPVE corrections to the relative energies of these isomers never exceeds 0.18 kcal mol⁻¹.

Although line broadening in the ^{13}C NMR spectra of 1,7,9-trioxadispiro[5.1.5.3]hexadecane suggests that **3E** may be the most stable cis isomer,[8] all computational results presented here indicate that **3E** is not likely to be present, to any appreciable extent, at equilibrium. Both **3B** and **3C** are at least 1 kcal mol⁻¹ more stable than **3E** in THF, DCM, acetone, and DMSO. Furthermore, the relative energies of both **3B** and **3C** in the solvent are in good agreement with the experimental values that range from 0.7 kcal mol⁻¹ in nonpolar solvents to 0.3 kcal mol⁻¹ in polar solvents.[8] Also, since **3D,E,H** are nearly isoenergetic in acetone and DMSO, one would expect **3D,H** to be present with **3E** at equilibrium in polar solvents.

To shed some light on this discrepancy, the ^{13}C NMR chemical shifts have been calculated at the B3LYP/6-311+G(*d*) level in the gas phase, in chloroform, and in DMSO for the five lowest energy isomers, **3A−E**. (See Supporting Information.) The C_2 symmetric **3A** isomer gives rise to seven unique signals, as does the C_s symmetric **3B** isomer which is qualitatively consistent with experimental observations. In contrast, the GIAO calculations predict that the other isomers (**3C−E**) will have far more than seven (up to 13) well resolved peaks in their ^{13}C NMR spectra, although rapid conversion between equivalent conformations could reduce the number of peaks observed.

Quantitatively, the ^{13}C NMR signals from the isomers of 1,7,9-trioxadispiro[5.1.5.3]hexadecane are quite similar. In the experimental spectrum, five of the peaks from the cis isomer differ from the corresponding trans signals by no more than 0.30 ppm and by as little as 0.04 ppm.[8] (The experimental chemical shifts have been tabulated in Supporting Information for convenience.) In only the signals assigned to the C5:C13 and C14:C16 pairs, the cis and trans peaks differ appreciably (by 1.35 and 1.32 ppm, respectively). The theoretical ^{13}C NMR spectra from GIAO calculations are similarly congested. Consequently, the typical theoretical procedure[24] for distinguishing between different configurational and conformational isomers on the basis of NMR chemical shifts fails even after empirically adjusting the B3LYP GIAO chemical shifts.[25] For example, when comparing the theoretical ^{13}C NMR spectra for **3B,D,E** to the experimental signals assigned to the cis isomer, one finds that all three sets of computed peaks differ from the experimental results by essentially the same amount. The average absolute deviations associated with the three theoretical spectra are essentially identical (differ by no more than 0.35 ppm), as are the maximum absolute deviations (differ by no more than 0.73 ppm) regardless of the environment (gas phase, chloroform, or DMSO). In other words, the typical scaling[25] and statistical analysis[24] of calculated ^{13}C NMR chemical shifts cannot definitively associate a particular isomer with the observed cis signals despite the fact that **3B** is the only cis isomer that is qualitatively consistent with the experimental spectrum.

Before concluding, the evidence in favor of **3B** and that against **3E** must be tempered with two caveats. There is an apparent inconsistency between the chair conformation of **3B** and the observed line broadening,[8] and our NMR computations do not include the dynamical effects necessary to model this phenomenon. Also, since the trans isomer **3C** is nearly isoenergetic with the cis isomer **3B**, it is possible that **3C** would be present if equilibrium between all of the thermodynamically accessible conformations of 1,7,9-trioxadispiro[5.1.5.3]hexadecane is established. We are currently collaborating with an experimental group to resolve these issues with more sophisticated NMR techniques.

4. Conclusions

Conformer **2A** is substantially more stable than all other structures of 1,7-dioxaspiro[5.5]undecane which is consistent with experimental observations[7] as well as the energetic model of Deslongchamps and co-workers.[6] Even in polar solvents, **2B** is at least 2.6 kcal mol⁻¹ above the global minimum, and the other conformers examined lie more than 4.5 kcal mol⁻¹ above **2A**.

The situation is rather different for 1,7,9-trioxadispiro[5.1.5.3]-hexadecane where several isomers within 2 kcal mol⁻¹ of the global minimum have been identified. Isomer **3A** is clearly the most stable isomer which is consistent with earlier work of McGarvey et al.[8] In polar solvents, **3B,C** lie only about 0.5 kcal mol⁻¹ above **3A** while $\Delta E \approx 1.7$ kcal mol⁻¹ for **3D,E,H**.

In contrast to the experimental assignment based on ^{13}C NMR spectra, this work indicates that **3B** is the most stable cis isomer, not **3E**. Not only is the relative energy of **3B** quantitatively consistent with the experimental cis:trans ratios, but also its ^{13}C NMR spectrum has only seven signals which is qualitatively consistent with the experimental spectrum. Other than **3C**, which is energetically very similar to **3B**, no other isomers (including **3E**) should be present to any appreciable extent at equilibrium under ambient conditions.

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