Synthesis and rotation barriers in 2, 6-Di-(o-anisyl) anisole

Takuhei Yamamotoa, Pi-Yu Chena, Guangxin Linb, Neil E. Jacobsena, Thomas Ballyb* and Richard S. Glassa*

Variable temperature 1H NMR spectroscopic studies of 2, 6-di(o-anisyl) anisole show syn and anti atropisomers at low temperature. The barrier for interconverting these isomers by rotation about the aryl-aryl bond, found by fitting the experimental data, is 41.2 kJ/mol.

Keywords: conformational analysis; dynamic NMR; quantum chemical calculations

INTRODUCTION

We recently reported11 atropisomerism in certain m-terphenyl thi- seleno- and telluro- ethers, such as 1a-c. The barriers for interconversion of the two syn and the anti atropisomers, respectively, were determined by variable temperature NMR spectroscopic studies.

The barriers for this interconversion increase on going from S to Se to Te that is, 1a → 1b → 1c. Calculations on 1a and 1b revealed that these barriers are due to rotation about the aryl-aryl bonds. Furthermore, the magnitude of this barrier is determined by the increase in the size of the chalcogen (S<Se<Te) and not by that of the length of the aryl-chalcogen bond (S-C<Se-C<Te-C). Notably absent from this study was the first-row chalcogen: oxygen. Since little work has been reported2–5 in these and related systems involving oxygen, we have synthesized and studied anisole derivative 1d and the results are reported in this note.

RESULTS AND DISCUSSION

Cram and coworkers20 first synthesized 1d, from bromodibenzofouran and Dyker and Kellner27 made it in modest yields in a mixture of products formed in an interesting Pd-catalyzed cascade reaction from 2-iodoanisole. We synthesized 1d, using a Suzuki coupling reaction28 as shown below:

The 1H and 13C NMR spectra for 2,6-di-(o-anisyl)anisole were fully assigned on the basis of analysis of 1D and 2D NMR spectra.

The 2D NMR spectra are found in the Supporting Information. The two singlets at δ 3.143 and 3.816 were assigned to hydrogens of the methoxy groups on the central ring and the outer ring, respectively, based on their chemical shifts and integrations. The methoxy protons showed correlations in the heteronuclear single quantum coherence (HSQC) spectrum, which allowed assignment of the signals at δ 56.00 and δ 60.75 in the 13C NMR spectrum to the outer ring and the center ring, respectively. The COSY correlations indicated the protons at δ 7.147 and 7.231 are in the same ring and are assigned to H4 and H3,5 on the basis of the AB2 splitting pattern and relative integrated areas. Crosspeaks in the HSQC spectrum of H4 with C4 and H3,5 with C3,5 allowed the assignment of the signal at δ 123.17 and that at δ 131.66 to C4 and C3,5, respectively. The heteronuclear multiple bond correlation (HMBC) spectrum showed the methoxy protons on the center ring and on the outer ring correlates with quaternary carbons bound to each of the oxygens and hence assigned to C1 (δ 157.45) and C2 (δ 156.72) and C2' (δ 157.45), respectively. The signal at δ 132.54 in the 13C NMR spectrum showed correlation with H4, but because there was no crosspeak in HSQC, this absorption was assigned to C2,6. In the 1H NMR spectrum, on the basis of the chemical shifts due to the methoxy group and the observed splitting patterns, H3,5 and H4' correlations in the HSQC spectrum, could be assigned to the signals at δ 7.016, 7.018, 7.293, and 7.357, respectively. On the basis of correlations of these signals in HSQC C3' (δ 111.34), C5' (δ 120.79), C6' (δ 131.85), and C4' (δ 129.23), signals could be assigned as shown. These assignments were further confirmed by crosspeaks in the ROESY spectrum of H3'/OCH3 in the...
Interestingly, only one peak is observed for the methoxy group appended to the central ring in 1d at the lowest temperature recorded, whereas 1a-c show two signals for the SMe, SeMe and TeMe moieties, respectively, below their coalescence temperature. Apparently, the difference in chemical shifts for the OMe groups of the central ring for the syn and anti atropomers is not resolved in our experiments. Note that, as before, there are three possible atropomers: one anti and two syn isomers, but evidence is obtained for only two. This presumably results from rapid rotation about the aryl-O bond of the central ring.

**Molecular Modeling**

The structures of all three atropomers and the transition states between them were optimized by the B3LYP/6-31G* and the B2LYP-D/cc-pVDZ methods. The calculated structures are depicted in the Figure 3 (and in Table S2 of the Supporting Information, along with the three important dihedral angles). It is worth noting that there are two transition states for the automerization of the anti conformers which are attained when the central-OMe group rotates towards one of the two lateral-OMe groups. However, the energy differences between these two transition states is less than 3 kJ/mol, and we will only consider the lower of the two, which appears in Figure 3. (In Figure S8 and Table S1 of the Supporting Information both transition states are shown). There is only one transition state between the two syn conformers because both of them have a plane of symmetry.

The relative enthalpies and free energies of the minima and transition states shown in Figure 3 are listed in Table 1. They were calculated both in the gas phase and in CH2Cl2 as a dielectric continuum solvent, but the results obtained from the two sets of calculations do not differ significantly. They show that the barriers for rotation around the central Ph-OMe bond, i.e. for the syn-a → syn-s interconversion and for the automerization of the anti conformer, are too low for these processes to be detected in the temperature range that is accessible in our NMR experiments, i.e. rapid equilibration between the syn-a and syn-s conformers is to be expected.

We have previously reported[13] that these barriers decrease on going from X = S (1a) to X = Se (1b) and we had attributed this to the increase of the C-X bond length, which leads to a concomitant increase of the distance between the Me that is attached to chalcogen and the lateral phenyl group. By this logic the barrier for rotation of the lateral phenyl group should be the highest for X = O (1d), but our present results show that this is not the case (the gas phase activation enthalpy for the syn-a → syn-s interconversion, calculated by the same method, is 19.4 kJ/mol for 1a and 16.5 kJ/mol for 1b. The corresponding numbers for the anti automerization are 19.0 and 15.3 kJ/mol, respectively).

We attempted to single out a reason for these peculiar trends by model calculations on the fragments from which compounds 1 are composed. These calculations showed that the steric repulsion between the Me group and the lateral phenyl group changes by less than 1 kJ/mol along the series. The distortion of the central Ph-X-Me moiety in the transition state, relative to optimized structures, does show an increase on going from X = O to X = S and a decrease on going to X = Se, but this effect accounts only for about a third of the total change. Thus we conclude that the observed trends are due to a combination of causes which cannot be easily disentangled.

On the other hand, the calculated barriers for converting the syn-a or syn-s to the anti conformers, i.e., for rotation of a lateral phenyl group, are much higher than the barriers for rotating...
the central O-Me moiety, and the calculated ΔG° are in excellent accord with the experimental free energy of activation of 41.2 kJ/mol. For 1d these barriers are lower than for 1a and 1b as it was expected according to interpretation given previously.[1]

Based on the geometries from B2PLYPD/cc-pVDZ calculations, the 1H NMR chemical shifts for the O-Me moieties were calculated following the protocol outlined in ref 21 (see Table 2). The predicted chemical shifts for the lateral -OMe groups are within 0.1 ppm of the experimental values, while for the central -OMe groups they are off by about 0.2 ppm. If we assume that rotation around the central Ph-OMe bond is rapid on the NMR timescale, i.e. the signals of the two syn conformers are averaged, even at −84°C, then the signals for the central OMe group should almost coincide (2.89 ppm for the averaged syn-, and 2.91 ppm for the anti conformer), which may explain why only one signal is seen for these protons. With

Table 1. Relative Energies in kJ/mol of Different Atropisomers of 1d and Barriers for Their Interconversion (See Figure 3 and Table S1 in the Supporting Information for Structures).

<table>
<thead>
<tr>
<th>conformer</th>
<th>H_rel</th>
<th>G_rel</th>
<th>H_rel</th>
<th>G_rel</th>
</tr>
</thead>
<tbody>
<tr>
<td>syn-s</td>
<td>1.13</td>
<td>0.44</td>
<td>1.39</td>
<td>0.60</td>
</tr>
<tr>
<td>syn-a</td>
<td>0.96</td>
<td>1.16</td>
<td>(0)</td>
<td>0.10</td>
</tr>
<tr>
<td>anti</td>
<td>(0)</td>
<td>(0)</td>
<td>0.10</td>
<td>(0)</td>
</tr>
<tr>
<td>TS(syn-a → syn-s)</td>
<td>13.90</td>
<td>20.90</td>
<td>12.16</td>
<td>19.16</td>
</tr>
<tr>
<td>TS(syn-s → anti)</td>
<td>32.70</td>
<td>42.57</td>
<td>32.46</td>
<td>42.33</td>
</tr>
<tr>
<td>TS(anti → syn-a)</td>
<td>33.82</td>
<td>43.88</td>
<td>33.61</td>
<td>43.67</td>
</tr>
<tr>
<td>TS(anti → anti)</td>
<td>15.09</td>
<td>21.84</td>
<td>13.01</td>
<td>19.75</td>
</tr>
</tbody>
</table>

*Calculated by the B2PLYP-D/cc-pVDZ method, using B3LYP/6-31G* thermal corrections and entropies.

Table 2. Calculated 1H NMR Spectroscopic Chemical Shifts for O-Me groups in 1d

<table>
<thead>
<tr>
<th>isomer</th>
<th>δ O-Me (central) (ppm)</th>
<th>δ O-Me (1) (ppm)</th>
<th>δ O-Me (2) (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>syn-a</td>
<td>2.85</td>
<td>3.90</td>
<td>3.90</td>
</tr>
<tr>
<td>syn-s</td>
<td>2.94</td>
<td>3.81</td>
<td>3.81</td>
</tr>
<tr>
<td>anti</td>
<td>2.91</td>
<td>3.81</td>
<td>3.85</td>
</tr>
</tbody>
</table>

*using the GIAO/ WP04/cc-pVDZ method with CH2Cl2 as a continuum solvent, and the scaling factors given in ref 21.
regard to the OMe groups on the lateral phenyl rings, averaging is predicted to lead to a signal at 3.83 ppm for the for the anti conformer and one at 3.86 ppm for the two syn-conformers, under conditions where the syn- and anti-conformers do not interconvert rapidly on the NMR time scale. Although the absolute chemical shifts are off by ca. 0.08 ppm (which is well within expectations from these calculations), their difference is in good accord with the observed Δδ = 0.026 ppm. The fact that the anti-conformer is predicted to predominate in the equilibrium, may explain why at −84 °C the signal at lower field is more intense than the other one (see Fig. 2).

METHODS

General

All reactions were performed using standard Schlenk techniques under an atmosphere of argon. Dioxane was purified by distillation under nitrogen from potassium-benzophenone ketyl. Column chromatography was done using 32–63 μm flash silica gel following the method of Still et al.[11] All mp are uncorrected. All 1H variable-temperature and 13C NMR spectra were obtained using an NMR spectrometer operating at a 1H frequency of 299.956 MHz, using a 5 mm Four-Nucleus probe. The ambient temperature without heating or cooling was 22 °C. NMR chemical shifts and coupling patterns in the aromatic rings were elucidated by simulation and curve fitting using WinNMR version 7.1.12 (Reich, H. J., University of Wisconsin, Madison, WI). Low-temperature experiments used dry nitrogen gas cooled to 77 K in a heat exchanger, and temperatures were calibrated using the 1H shift separation of a methanol sample: T(δ(K)) = 409.0 - 36.54 x - 21.85 x² where x is the chemical shift difference in ppm between CH3 and OH proton resonances.[23] All 1H NMR spectra are referenced to residual solvent at δ 5.32 ppm (CDCl3), and all 13C NMR spectra are referenced to deuterated CD3Cl at δ 4.00 (CD3Cl).

High resolution MS were obtained by direct insertion. All reactions were performed using standard Schlenk techniques under an atmosphere of argon. Dioxane was purified by distillation under nitrogen from potassium-benzophenone ketyl. Column chromatography was done using 32–63 μm flash silica gel following the method of Still et al.[11] All mp are uncorrected. All 1H variable-temperature and 13C NMR spectra were obtained using an NMR spectrometer operating at a 1H frequency of 299.956 MHz, using a 5 mm Four-Nucleus probe. The ambient temperature without heating or cooling was 22 °C. NMR chemical shifts and coupling patterns in the aromatic rings were elucidated by simulation and curve fitting using WinNMR version 7.1.12 (Reich, H. J., University of Wisconsin, Madison, WI). Low-temperature experiments used dry nitrogen gas cooled to 77 K in a heat exchanger, and temperatures were calibrated using the 1H shift separation of a methanol sample: T(δ(K)) = 409.0 - 36.54 x - 21.85 x² where x is the chemical shift difference in ppm between CH3 and OH proton resonances.[23] All 1H NMR spectra are referenced to residual solvent at δ 5.32 ppm (CDCl3), and all 13C NMR spectra are referenced to deuterated CD3Cl at δ 4.00 (CD3Cl). High resolution MS were obtained by direct insertion.

Synthesis of 2,6-di(α-anisylanisole, 1d

The method reported by Azzena and co-workers[22] for Suzuki coupling was used with slight modification. To a solution of 1,3-dibromo-2-methoxybenzene[13,14] (300 mg, 1.13 mmol) in 1,4-dioxane (1.5 mL) under Ar, were added a 2M aqueous solution of Na2CO3 (1.13 mL, 2.26 mmol), LiCl (153 mg, 3.61 mmol), 2-methoxyphenylboronic acid (686 mg, 4.5 mmol), and Pd(PPh3)4 (130 mg, 0.113 mmol). This mixture was stirred and heated at reflux for 24 h. After cooling to room temperature, H2O (20 mL) was added to the suspension. The aqueous layer was extracted with EtOAc (3 X 20 mL). The combined organic layers were washed successively with 1M aqueous NaOH (50 mL), brine (50 mL), and H2O (50 mL). The organic layer was dried (MgSO4) and then concentrated under reduced pressure. The residue was purified by silica gel chromatography using hexanes:chloroform (1:1) and then chloroform to elute 1d as a white solid (160 mg, 44%). The product was further purified by recrystallization twice from diethyl ether:hexanes (1:1): mp 118-119 °C (lit. 117-118 °C); 1H NMR (500 MHz, CD2Cl2) δ 3.143 (s, 3H), 3.816 (s, 6H), 7.016 (dd, J = 8.3, 1.2 Hz, 2H), 7.018 (dt, J = 1.1, 7.6 Hz, 2H), 7.147 (A, 1H) and 7.231 (B, 2H), AB2 system (JAB = 7.6 Hz), 7.293 (dd, J = 7.7, 1.8 Hz, 2H), 7.357 (ddd, J = 8.2, 7.5, 1.8 Hz, 2H), 13C NMR (125 MHz, CD2Cl2) δ 56.00, 60.75, 111.34, 120.79, 123.17, 128.61, 129.23, 131.66, 131.85, 132.54, 156.72, 157.45; IR (KBr) 2934, 2833, 1581, 1491, 1465, 1272, 1237, 1025, 756 cm⁻¹; HRMS (GC MS EI⁺, m/z): Calcd for C21H20O3, 320.1412; Found: 320.1412.

Variable temperature NMR studies

CD2Cl2 was used as the solvent. The 1H NMR exchange line fitting results were obtained using WinNMR version 7.1.14 (Reich, H.J., University of Wisconsin, Madison, WI). The spectra used for fitting were acquired just below the coalescence temperature for the resonance being fitted in order to maximize the information content. Line widths were determined by fitting peaks well below the coalescence temperature where exchange broadening is negligible. Chemical shifts and relative peak areas of the two conformers, as well as the exchange rate constants were obtained by visual fit to the experimental data. The conformer present in greater concentration just below coalescence is referred to as the “A” conformer, and the other conformer is described as “B”. The free energy of activation was calculated using the equation: ΔG° = [23.76 - ln(k/T)]RT.[15]

Quantum chemical calculations

Geometry optimizations and frequency calculations were first done with the B3LYP/6-31G* method, where all stationary points (minima, transition states) were properly characterized and thermodynamic functions were calculated. Geometries were then reoptimized with the recently introduced “double hybrid” B2PLYP functional,[16] corrected for contributions of dispersion energy,[17,18] which accounts much better for steric interactions than pure DFT functionals do. As analytic second derivatives were not yet available for the B2PLYP method, we used the thermal corrections and entropies from B3LYP calculations in the evaluation of the relative enthalpies and free energies listed in Table 1. Finally, single-point SCRF calculations in CH2Cl2 as a continuum solvent were done, with the B2PLYP-D functional at the corresponding geometries, to evaluate relative enthalpies and free energies in solution. NMR chemical shifts were calculated using the GIAO method and the WP04 functional that was developed with that purpose in mind,[19,20] using the cc-pVDZ basis set. SCRF calculations were again carried out in CH2Cl2 as solvent and the raw isotropic magnetic shieldings (IMS) were converted to chemical shifts relative to TMS δ by scaling them with the parameters elaborated recently by Jain et al.[21] (δ = 31.844 – (IMS/1.0205)). All calculations were done with the Gaussian program package.[22]

Acknowledgements

We gratefully acknowledge financial support of this work by the U.S. National Science Foundation (CHE-0956581, R.S.G.) and the Swiss National Science Foundation (Project 2000–121747, T.B.)

REFERENCES

In one syn isomer the O-Me group of the central ring is facing away from the MeO groups and in the other the O-Me group is facing toward the MeO groups.

In Gaussian, the WP04 functional is invoked by specifying the BLYP keyword and adding iop(3/76=1000001189,3/77=0961409999,3/78=0000109999) to the keyword line.