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# Synthesis, Structure and AM1 Conformational Study of 1,12-Dioxa-2,11-dioxo[3.3]orthocyclophane.

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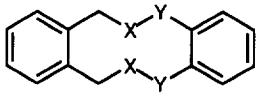
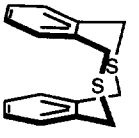
*Abstract*: The title compound was synthesized by a two-fold BOP-Cl mediated esterification of *o*-phenylenediacetic acid with catechol. The presence of the bridging esters results in a considerable change in the conformational landscape of the cyclophane system in comparison to the parent [3.3]orthocyclophane and related systems. A conformer search at the AM1 level identified six low energy conformers. The one observed in the solid state was calculated to be the second lowest in energy, 0.32 kcal/mol above the calculated global minimum.


We have recently become interested in preparing [3.3]cyclophanes containing ester units in their bridges and in evaluating their potential as precursors to smaller, functionalized cyclophanes *via* intramolecular Fries rearrangements. In addition, the presence of bridging esters might be expected to result in marked changes in the conformational behavior compared to their parent systems. We now report the synthesis of 1,12-dioxa-2,11-dioxo[3.3]orthocyclophane **1**, the first member of this class of cyclophane.

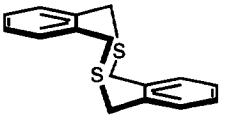
The first report of a [3.3]orthocyclophane was in 1979 by Au *et al* who described the synthesis of 2,11-dithia[3.3]orthocyclophane **2**.[1] Nearly a decade then passed before a conformational study of **2** was published by Lai and Nakamura,[2] who concluded that the *syn,chair,chair* conformer *syn*-**2** (Figure 1) was the most stable in solution. Fukazawa *et al.*[3] then showed that the preferred solid state geometry was an *anti* conformer, *anti*-**2** and presented a combination of molecular mechanics calculations and an estimate of the secondary induced magnetic field due to an aromatic ring current[4] to suggest that this was also the case in solution. These authors also drew the same conclusions for the diselena analog **3**.[3] Subsequent work by Hopf *et al.*[5,6] was consistent with these findings. However, the dioxa analog **4**[7] was predicted to prefer an anticlinal conformation *anti*-**4** in solution. The parent [3.3]orthocyclophane **5** and its 2,2,11,11-tetradeuterio analog **6** were finally reported in 1993 by Fukazawa *et al.*[8] and an *anti* conformer analogous to *anti*-**2** was concluded to be the lowest in energy.



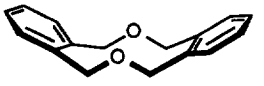

**1** X = CO, Y = O
**2** X = S, Y = $CH_2$
**3** X = Se, Y = $CH_2$
**4** X = O, Y = $CH_2$
**5** X = Y = $CH_2$
**6** X = $CD_2$, Y = $CH_2$




*syn*-**2**




*anti*-**2**



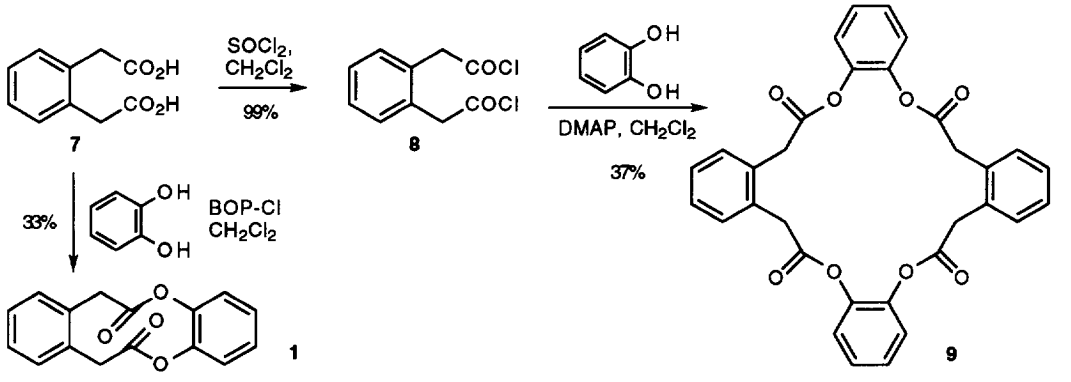

*anti*-**4**

Figure 1.

Our first approach to the synthesis of **1** involved conversion of diacid **7** into diacid chloride **8** (99%) upon treatment with thionyl chloride (Scheme 1). However, slow addition (9 h) of a mixture of **8** and catechol to a refluxing solution of DMAP in dichloromethane afforded only the macrocyclic tetrakis(lactone) **9**[9] in 37% yield. Although a small amount of the desired cyclophane **1** was observed by tlc during the course of the reaction, none of this compound was isolated after column chromatography.

The product distribution was essentially reversed when diacid **7** was esterified with catechol in the presence of BOP-Cl.[10,11] In this case, cyclophane **1**[12] was isolated as the only non-polar product in 33% yield. None of the tetraester **9** was isolated, although its presence was detected by tlc analysis of the crude reaction mixture. Worthy of note is that **1** appears to be quite susceptible to hydrolysis during chromatography. Best yields were obtained when thoroughly dried silica was employed.

The bridge protons of both **1** and **9** appear as a singlet at $\delta$ 3.98 in their respective $^1$H NMR spectra. No significant broadening was observed in either case upon cooling to -90 °C, indicating facile conformational mobility involving exchange of the diastereotopic benzylic hydrogens in both systems. The carbonyl stretching frequencies in **1** (1760, 1746 cm$^{-1}$) and **9** (1756 cm$^{-1}$) are typical for phenolic esters and this is consistent with the absence of significant strain in either molecule.




Scheme 1.

Single crystal X-ray analysis[13] of **1** (Figure 2) revealed that an unprecedented twisted anticlinal conformation (*vide infra*) with $C_i$ symmetry had been adopted in the solid state. There are no significant deviations from planarity in the aromatic rings. The torsion angle C(3)-C(4)-C(9)-C(10) is, with experimental error, 0°, but that of O(1)-C(18)-C(13)-O(12) is 6.4(8)°. No other unusual structural features were apparent.

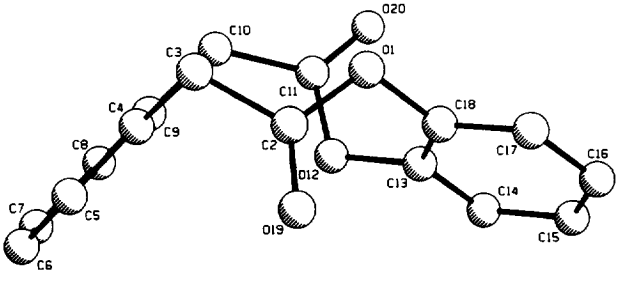



Figure 2. Molecular structure of **1** in the crystal. Selected bonds lengths (Å) and angles (°): O(1)-C(2) 1.369(7), C(2)-O(19) 1.193(8), C(2)-C(3) 1.498(8); C(18)-O(1)-C(2) 114.0(5), O(1)-C(2)-O(19) 123.1(7), O(1)-C(2)-C(3) 112.2(6), C(2)-C(3)-C(4) 109.3(6).

A conformer search allowing for rotation about all of the bridge bonds was performed on **1** using the Spartan software package at the AM1 level and six low energy conformers **1A-1F** were identified (Figure 3). The lowest energy conformer **1A** corresponds to that predicted for **4**.[7] This conformer was also calculated to be a low energy conformer of **2** (2.8 kcal/mol above the lowest energy conformer) and a high energy (11.4 kcal/mol) conformer of **5**.[8] Conformer **1D** also closely resembles a high energy (7.2 kcal/mol) conformer of **5**.[8] Conformers **1E** and **1F** bear some resemblance to the low energy *anti* conformers of **2**,[3] **3**,[3] and **5**.[8] The remaining conformers **1B** (the solid state conformer) and **1C** are without precedent in [3.3]orthocyclophane chemistry. This is most likely a consequence of the presence of $sp^2$-hybridized atoms in the bridges.

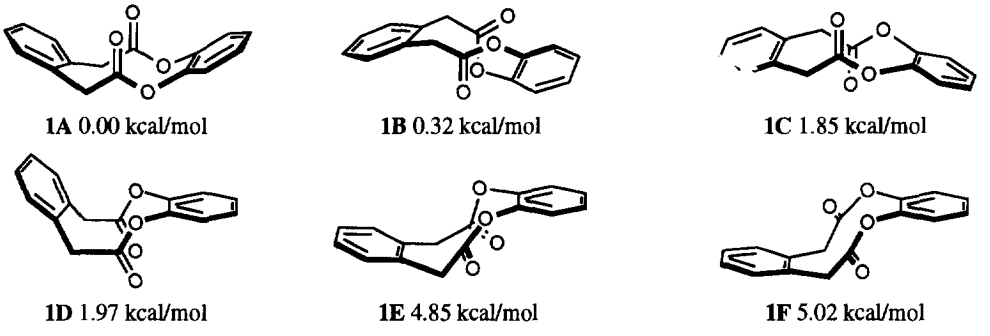



Figure 3. Calculated low energy conformers of **1** (energies are reported relative to the lowest energy conformer).

The small calculated energy differences between **1A-1D** suggest that these four conformers are all present in significant proportions in solution, whereas **1E** and **1F** would be expected to be much less prevalent. Interconversion between all of these conformers can occur by rotation of the bridge bonds, but none of these processes results in an exchange in the environments of the diastereotopic benzylic hydrogens. For this to occur, an interconversion between **1A** and **1A'** (Figure 4), or any other conformer and its counterpart, must be in operation. With no significant line broadening of the benzylic signal in the $^1$H NMR spectrum of **1** at -90 °C, this process has a free energy of activation of < 9.5 kcal/mol (assuming a very small $\Delta\nu$ value of 10 Hz).


Figure 4.

In summary, 1,12-dioxa-2,11-dioxo[3.3]orthocyclophane **1** can be conveniently synthesized in a one step BOP-Cl mediated esterification. Work aimed at the synthesis and study of other [3.3]cyclophanes with esters incorporated into their bridges is now underway.

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## REFERENCES AND NOTES


1. Au, M.-K.; Mak, C. W.; Chan, T. L.*J. Chem. Soc., Perkin Trans. 1* **1979**, 1475-1477.
2. Lai, Y.-H.; Nakamura, M. *J. Org. Chem.* **1988**, *53*, 2360-2362.
3. Okajima, T.; Wang, Z.-H.; Fukazawa, Y. *Tetrahedron Lett.* **1989**, *30*, 1551-1554.
4. Fukazawa, Y.; Ogata, K.; Usui, S. *J. Am. Chem. Soc.* **1988**, *110*, 8692-8693.
5. Bodwell, G.; Ernst, L.; Hopf, H.; Jones, P. G. *Tetrahedron Lett.* **1989**, *30*, 6005-6008.
6. Jones, P. G.; Bodwell, G.; Hopf, H. *Z. Naturforsch.* **1990**, *45b*, 1213-1215.
7. Okajima, T.; Wang, Z.-H.; Fukazawa, Y. *Chem. Lett.* **1991**, 37-40.
8. Wang, Z.-H.; Usui, S.; Fukazawa, Y. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 1239-1243.
9. **9**: m.p. 252-255 °C; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ = 7.37 (8H, AA'BB'), 7.17 (8H, AA'BB'), 3.98 (8H, s); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ = 168.8, 141.8, 132.6, 130.9, 128.2, 126.6, 123.3, 38.5; MS (EI, 70 eV) m/z (%) = 536 (4), 427 (14), 269 (32), 241 (16), 233 (36), 205 (17), 159 (33), 158 (33), 131 (79), 110 (29), 104 (72), 103 (100); IR (nujol) $\nu_{max}$ = 1756 (s) cm$^{-1}$.
10. Diago-Meseguer, J.; Palomo-Coll, A. L.; Fernández-Lizarbe, J. R.; Zugazo-Bilbao, A. *Synthesis* **1980**, 547-551. See also Corey, E. J.; Hua, D. H.; Pan, B.-C.; Seitz, S. P. *J. Am. Chem. Soc.* **1982**, *104*, 6818-6820; Scherkenbeck, J.; Plant, A.; Harder, A.; Mencke, N. *Tetrahedron* **1995**, *51*, 8459-8470; Bartra, M.; Urpí, F.; Vilarrasa J. in *Recent Progress in the Chemical Synthesis of Antibiotics and Related Microbial Products, Vol. 2*, Ed. Lukacs, G. Springer-Verlag, New York, 1993.
11. Experimental procedure for **1**: To a solution of BOP-Cl[10] (2.00g, 7.86 mmol) in dichloromethane (200 ml) at reflux was added a solution of *o*-phenylenediacetic acid **7** (0.529 g, 2.72 mmol), catechol (0.300 g, 2.72 mmol) and DMAP (2.00 g, 16.4 mmol) in dichloromethane (300 ml) over 9 h. After cooling, the crude mixture was passed through a plug of oven dried silica and the plug was washed with dichloromethane. The solvent was removed and the residue was chromatographed on oven dried silica / dichloromethane to give cyclophane **1** ($R_f$ = 0.65) as a colorless solid (0.244 g, 33%).
12. **1**: m.p. 191-193 °C; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ = 7.34 (4H, AA'BB'), 7.24 (4H, AA'BB'), 3.98 (4H, s); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ = 170.3, 144.1, 132.9, 132.3, 128.6, 126.7, 122.6, 40.6; MS (EI, 70 eV) m/z (%) = 268 (7), 159 (26), 158 (46), 131 (41), 110 (51), 104 (59), 103 (100); IR (nujol) $\nu_{max}$ = 1760 (s), 1746 (s) cm$^{-1}$.
13. X-ray data for **1**: colorless irregular crystal (approx. 0.15 x 0.15 x 0.40 mm) from dichloromethane/ hexanes $C_{16}H_{12}O_4$, M = 268.27, orthorhombic, $P2_12_12_1$ (#19), Z = 4, a = 13.200 (6), b = 19.716 (8), c = 4.934 (5) Å, V = 1284 (2) Å$^3$, $D_c$ = 1.388 g cm$^{-3}$, F(000) = 560, $\mu$ (Mo-K$\alpha$) = 0.93 cm$^{-1}$. Data collection with a Rigaku AFC6S diffractometer with graphite monochromated Mo-K$\alpha$ radiation ($\lambda$ = 0.71069 Å), $\omega$-2$\theta$ scan type with $\theta$ scan width (1.26 + 0.35 tan$\theta$)°, $\omega$ scan speed 4.0° min$^{-1}$ (2 rescans for weak reflections), 1377 reflections measured, empirical absorption correction (max., min. corrections = 1.00, 0.94), giving 828 with $I > 2\sigma(I)$. Solution and refinement by direct methods using the TEXSAN package of the Molecular Structure Corporation; the non-hydrogen atoms were refined either anisotropically or isotropically; full matrix least squares refinement with 122 variable parameters led to $R$ = 0.061 and $R_w$ = 0.43, GOF = 2.11. Further details of the crystal structure may be obtained from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, on quoting the full journal citation.


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