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An *in*-Ketocyclophane

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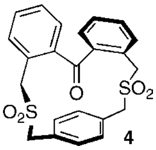
ABSTRACT



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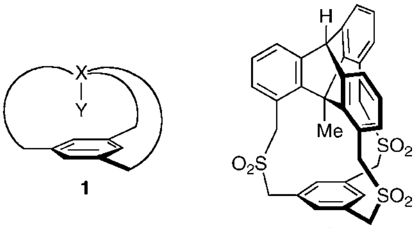
Computational studies indicate that some benzophenone-capped cyclophanes should have carbonyl groups pointed directly at their basal benzene rings as a result of conformational restraints imposed by bulky groups in the linking arms of the molecules. Cyclophane 4 was prepared, and its X-ray structure shows it to be the first *in*-ketocyclophane.

The preparation and characterization of compounds with very tight or unusual nonbonded interactions is a persistent theme in cyclophane chemistry, and for some 20 years we and others have pursued the synthesis of sterically congested *in*-cyclophanes bearing functional groups projected directly toward aromatic rings.[1] C_3-symmetric cyclophane frameworks (**1**) with inwardly directed apical functionality (X−Y) have been employed in most successful syntheses of this sort, and the list of projecting groups includes hydrogen atoms (X−Y = C−H, N−H, and Si−H),[2−4] lone pair electrons (N-lp, P-lp),[4−7] fluorine atoms (Si−F),[7] and methyl groups ($C-CH_3$).[8] All such cyclophanes may, in principle, exhibit *in/out* isomerism,[9] but in most cases a greater angle strain associated with the *out*-isomers causes the *in*-isomers to be formed exclusively in the final macrocyclization reactions. Only for the synthesis[8] of *in*-methylcyclophane **2** was an elaborate structure (the triptycene cap) required to block *out*-isomer formation, which had been observed in simpler frameworks.[7]

Carbonyl groups or, indeed, any oxygen atoms are notably lacking from the list of apical functionality. Having only two points of attachment at the carbon, carbonyls are unsuitable for incorporation into the preferred C_3 framework **1** (Figure 1). Although it is easy to imagine more highly branched structures that might serve to point a carbonyl group at an aromatic ring, the synthesis becomes most challenging. Is there a simpler approach?



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2

Figure 1. *in*-Cyclophanes.

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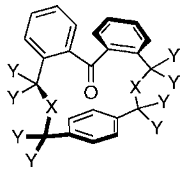
In this paper we report computational studies on a series of simple ketone-containing cyclophanes where increased rigidity and/or steric bulk in their connecting arms force the ketone groups to adopt *in*-conformations. We then report the synthesis and crystallographic characterization of the first *in*-ketocyclophane.

Diaryl ketones, such as benzophenone, tend to adopt C_2-symmetric conformations resembling two-bladed propellers, and the incorporation of such a structure into a cyclophane greatly restricts its conformational freedom. With the right choice of substituents and short linking arms to a basal aromatic ring, the ketone may be prevented from lying parallel to the basal ring, and ultimately forced to point directly at it. After screening numerous candidates at low levels of theory, several cyclophanes were found that appeared likely to adopt *in*-conformations, especially when the linking arms are highly substituted. The conformations and energies of the most promising series of molecules were examined at the HF/3-21G(*) and B3PW91/6-31G(d) levels of theory, and Table 1 summarizes these data.

Table 1. ZPE-Corrected Relative Energies for Conformations of Cyclophanes **3**−**5**



3 X = S, Y = H
4 X = SO_2, Y = H
5 X = SO_2, Y = Cl

conf	symmetry	ΔE [HF/3-21G(*)][a]	ΔE [B3PW91/6-31G(d)][a]	imag freq
3a	C_1	−2.73	−1.67	0
3b	C_1	−1.36	−1.50	0
3c	C_2	0.00	0.00	1
4a	C_1	−3.36	−1.71	0
4b	optimizes to **4c**			
4c	C_2	0.00	0.00	0
5a	C_1	6.22	5.65	0
5b	C_1	7.44	5.10	0
5c	C_2	0.00	0.00	0

[a] Relative energies are given in kcal/mol, and the relative energy of the C_2 conformation has been set to zero for each compound.

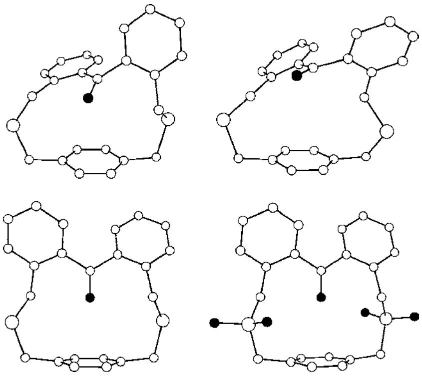
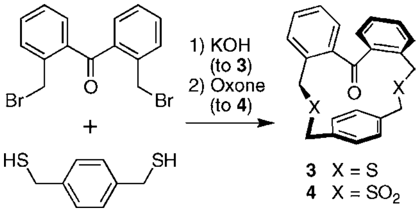


Figure 2. Calculated conformations of cyclophanes **3** and **4**. Clockwise from upper left: **3a**, **3b**, **4c**, and **3c**.

Compound **3** possesses only two accessible conformational minima, both with C_1 symmetry, and they are illustrated in Figure 2. In both cases the ketone lies roughly parallel to the basal aromatic ring. The C_2-symmetric *in*-cyclophane **3c** is not a minimum but rather a transition state for the interconversion of homochiral conformations of **3b**. The goal is to somehow make the transition state conformation the ground state! Oxidation of thioether **3** to disulfone **4** yields a different steric environment for the ketone. Although the first C_1 conformation (**4a**) remains the low energy structure, a clash of the sulfone oxygen atoms with the ketone oxygen eliminates the second C_1 conformation (**4b**) in favor of the desired C_2 conformation **4c** (Figure 2), which is now a potential minimum. In this structure the sulfone oxygen atoms flank the carbonyl group, reducing its conformational mobility, and the carbonyl group points directly at the center of the basal aromatic ring. However, this C_2 conformation (**4c**) remains slightly higher in energy (1.7 kcal/mol) than the C_1-symmetric, "*out*"-isomer **4a**, although both conformations would be present in solution. In order to guarantee that an *in*-ketone would be the dominant conformation, it is necessary to halogenate the side chain carbons. Addition of eight chlorine atoms to the linking arms gives cyclophane **5**, in which steric crowding forces the linkers to prefer an extended conformation, which in turn directs the ketone group to point at the basal ring. Thus the C_2 conformation of the octachlorocyclophane (**5c**) is strongly preferred (by >5 kcal/mol) over the two C_1-symmetric minima (**5a** and **5b**).

The key precursors of cyclophane **3** are readily available. 2,2′-Bis(bromomethyl)benzophenone, prepared in low yield as described by Cava and Kuczkowski,[10] and commercial 1,4-bis(mercaptomethyl)benzene were treated at high dilution with KOH to give **3** in 13% yield. This material was then oxidized with excess Oxone to give the relatively insoluble sulfone **4** in 89% yield (Scheme 1).

Scheme 1. Synthesis of Cyclophane **4**



3 X = S
4 X = SO_2

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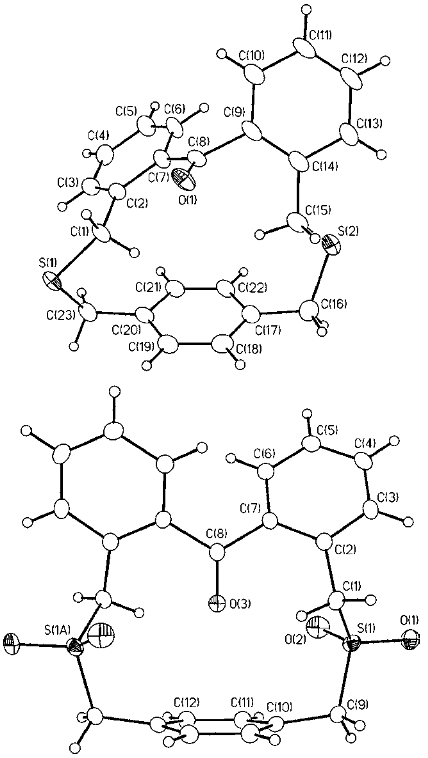

Figure 3. Molecular structures of cyclophanes **3** (top) and **4** (bottom) at 100 K (50% thermal ellipsoids have been employed).

Small, multiple crystals of compound **3** formed from solutions in a variety of solvents, but finally a sample suitable for X-ray analysis was obtained from chloroform/ethanol. In contrast, compound **4** readily crystallized upon diffusion of water into a DMSO solution. The molecular structures of both molecules were determined at 100 K, and they are illustrated in Figure 3. As expected, compound **3** adopts the calculated low-energy conformation **3a**. The flexible arms of this cyclophane allow the carbonyl group to lie almost parallel to the basal benzene ring, and there are no unusually close nonbonded contacts.

In contrast, compound **4** crystallized in the space group $C2/c$ (No. 15), and the molecule lies on a special position with crystallographic C_2 symmetry. Thus this cyclophane adopts the desired *in*-keto conformation **4c**, at least in the solid state! The structure very closely resembles the HF/3-21G(*)-calculated C_2 minimum: the crystallographic and calculated values of $d_{\mathrm{O-Ar}}$ are 2.91 and 2.94 Å, respectively, and the shortest O−C contacts [$d_{\mathrm{O-C}}$, in this case O(3)−C(10)] are 3.20 and 3.23 Å, respectively.[11] As we have previously observed,[1,12] common DFT methods overestimate such contacts. For the B3PW91/6-31G(d) structure of **4c**, $d_{\mathrm{O-Ar}} = 2.96$ Å and $d_{\mathrm{O-C}} = 3.25$ Å, and for the B3LYP/6-31G(d) structure, $d_{\mathrm{O-Ar}} = 3.00$ Å and $d_{\mathrm{O-C}} = 3.29$ Å, each almost 0.1 Å greater than the experimental value.

The crystal conformation (**4c**) is not the lowest energy conformation of **4** at any level of theory examined, although the relative energies are close. At the B3PW91/6-31G(d) level, conformation **4a** is 1.7 kcal/mol lower; at B3PW91/6-311+G(2d,p), 1.6 kcal/mol; at B3LYP/6-31G(d), 1.4 kcal/mol; and at B3LYP/6-311+G(2d,p), 1.2 kcal/mol. Thus it is probable that about 10% of the molecules of **4** adopt the *in*-keto conformation in solution, but interconversion of the two conformations is surely rapid at room temperature.

Compound **4** has a unique structure. The electron cloud of the ketone oxygen is projected into the π-cloud of the benzene ring. The closest contacts fall exactly at the sum of the van der Waals radii of carbon and oxygen (3.2 Å), so there is no great steric compression of the carbonyl group. The experimental C=O bond distance for **4** is normal [1.219 (3) Å] and not significantly different from that observed in cyclophane **3** [1.215 (4) Å]. The basal aromatic ring of **4** is slightly bowed outward, and this distortion likely accommodates most of the strain in **4**.

However, a comparison of the IR spectra (KBr) of compounds **3** and **4** gives evidence of some constraints on the *in*-keto group. The carbonyl stretching band for *in*-cyclophane **4** (1658 cm^{-1}) shows a frequency enhancement of 5 cm^{-1} when compared to that of **3** (1653 cm^{-1}). Although much smaller than the frequency enhancements of up to 400 cm^{-1} observed for C−H and Si−H stretches in several cyclophanes containing *in*-hydrogen atoms,[2,4] it does suggest that the stretching vibration of the carbonyl in **4** is restricted by the basal ring.

Whether structural relatives of **4** will contain more highly congested ketones is the subject of ongoing studies.

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Supporting Information Available: NMR spectra of compounds **3** and **4**, crystallographic information files in CIF format for **3** and **4**, and an ASCII text file containing the coordinates of the calculated structures of compounds **3**−**5** at the B3PW91/6-31G(d) level of theory. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) "$d_{\mathrm{O-Ar}}$" is the distance from the ketone oxygen atom to the centroid of the basal ring, and "$d_{\mathrm{O-C}}$" is the distance from the oxygen to a basal ring carbon atom.

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