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Macrocycle Ring Expansion by Double Stevens Rearrangement

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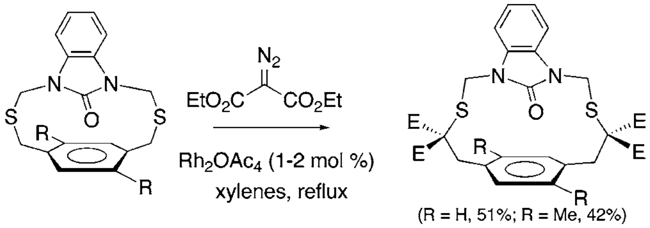
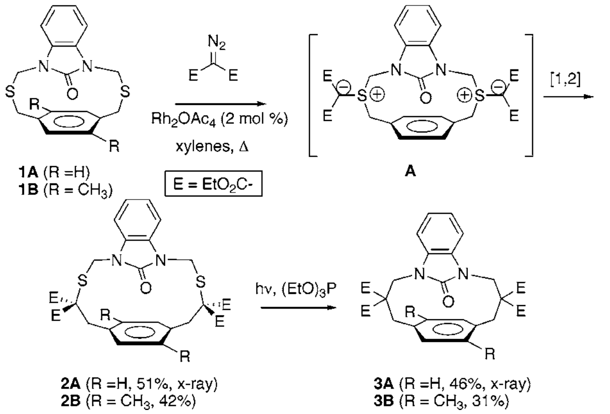
ABSTRACT



New benzimidazolidinone cyclophanes were synthesized through a double Stevens rearrangement employed as a ring expansion technique. Para-substituted heterophanes underwent efficient rearrangement. Meta-substituted heterophanes were also prepared. Structure analyses of the new cyclophanes are also provided.

Macrocycles with internal cavities and polar functionality provide useful platforms to model enzymatic reactions and to study complexation of small molecules; this approach has formed the foundation of host−guest chemistry using cyclophanes.[1] Because of their unique structure, cyclophanes continue to interest synthetic chemists and several catalytic applications employing cyclophane architecture have been recently reported.[2] We previously described the synthesis of novel heterocyclic cyclophanes (heterophanes) using transacetalization to furnish the macrocyclic ring.[3] The heterophanes contain a urea, a highly polar functional group suitable for metal binding which can serve as a hydrogen-bonding acceptor. In this report, we disclose a rhodium(II)-catalyzed double Stevens rearrangement used to enlarge the sulfur-containing macrocycles by two carbon atoms (Scheme 1). The insertion is highly regioselective and provides access to larger carbocyclic cyclophanes after sulfur atom extrusion.

Scheme 1. Ring Expansion by Double Stevens Rearrangement



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[1] Reviews: (a) Cram, D. J.; Cram, J. M. *Acc. Chem. Res.* **1971**, *4*, 204. (b) Diederich, F. *Cyclophanes (Monographs in Supramolecular Chemistry)*; RSC: Cambridge, 1991. (c) Dietrich, B.; Viout, P.; Lehn, J. M. *Macrocyclic Chemistry*; Wiley-VCH: Weinheim, 1993. (d) Gleiter, R., Hopf, H., Eds. *Modern Cyclophane Chemistry*; Wiley-VCH: Weinheim, 2004.

[2] (a) Pye, P. J.; Rossen, K.; Reamer, R. A.; Tsou, N. N.; Volante, R. P.; Reider, P. J. *J. Am. Chem. Soc.* **1997**, *119*, 6207−6208. (b) Zanotti-Gerosa, A.; Malan, C.; Herzberg, D. *Org. Lett.* **2001**, *3*, 3687−3690. (c) Gibson, S. E.; Knight, J. D. *Org. Biomol. Chem.* **2003**, *1*, 1256−1269. (d) Ma, Y.; Song, C.; Ma, C.; Sun, Z.; Chai, Q.; Andrus, M. B. *Angew. Chem., Int. Ed.* **2003**, *42*, 5871−5874. (e) Hua, J.; Lin, W. *Org. Lett.* **2004**, *6*, 861−864. (f) Song, C.; Ma, C.; Ma, Y.; Feng, W.; Ma, S.; Chai, Q.; Andrus, M. B. *Tetrahedron Lett.* **2005**, *46*, 3241−3244.

[3] Ellis, K. K.; Wilke, B.; Zhang, Y.; Diver, S. T. *Org. Lett.* **2000**, *2*, 3785−3788.

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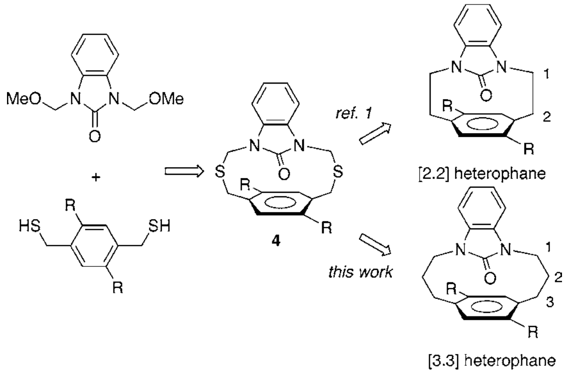
We also describe the synthesis of heterophanes featuring meta substitution on the aromatic ring.

Chemistry for *ring expansion* of cyclophanes has seldom been explored. For the synthesis of cyclophane-containing N-heterocyclic carbenes, we needed access to cyclophanes of varying ring size. To do this, a common heterophane[4] building block was an attractive starting point. To generate smaller, more strained cyclophanes, earlier cyclophane syntheses successfully employed the sulfur-mediated synthesis of dithiacyclophanes,[5] followed by ring contraction. A variety of methods for sulfur atom extrusion have been developed to yield the corresponding hydrocarbon [2.2]-cyclophanes. Our group developed a new method to make heterophanes assembled by acid-catalyzed transacetalization to form the macrocycle bis-*N,S*-acetal **4** (Scheme 2).[6] We considered whether the heterophane intermediate **4** could be manipulated into larger macrocycles, such as heterophanes with three carbons in the bridges (Scheme 2). This process requires intercalation of a carbon into each bridge of the macrocycle.

Scheme 2. Dithiamacrocycle **4** as an Intermediate



Because the dithiacyclophanes feature a reactive site at the nucleophilic sulfur atoms, metal carbenes might attack the sulfur atoms and provoke a Stevens rearrangement.[7] To the best of our knowledge, the Stevens rearrangement has not been used to expand heterophanes via sulfonium ylides.[8] Early work by Ando suggests that sulfur ylides are intermediates in this process;[9] in some cases, they can be isolated.[9b] Sulfonium ylides have been used in a [2,3] sigmatropic ring expansion protocol for medium ring carbocycle synthesis in elegant work by Vedejs.[10]

The double Stevens rearrangement worked well for the benzimidazolidinone ring expansion (Scheme 1). The thiacyclophanes **1** were prepared as reported previously.[3] Diazomalonate was slowly added to a solution of **1A** containing a catalytic amount of Rh_2OAc_4 in refluxing xylenes. Rearrangement of both homologues took place in good yield.[11] The balance of the mass in the Stevens rearrangement is ca. 15% unidentified byproducts,[12] and the rest is intractable polymer. Diazo decomposition occurred at lower temperatures (refluxing 1,2-dichloroethane and benzene solvents), but the [1,2] ring expansion had not taken place. Instead, a white precipitate was obtained, consistent with the bissulfur ylide **A** (the intermediate depicted in Scheme 1). When the intermediate was isolated and subsequently heated for 3 h in xylenes, conversion to **2A** was observed.

The ring-expanded cyclophanes underwent photochemical extrusion of the bridging sulfur atoms to give ring-contracted [3.3]heterophanes. A dilute solution of the [4.4]dithiacyclophane **2** in distilled triethyl phosphite was irradiated with a medium-pressure Hg lamp (Hanovia). These photochemical extrusions worked surprisingly well, possibly because of the lower ring strain relative to the [2.2]heterophanes synthesized previously by this method[3] (see also the *meta*-cyclophanes, vide infra). Comparable literature examples report very low yields in photochemical extrusion steps for making similar hydrocarbon cyclophanes.[13]

The structure of the [4.4]dithiacyclophane **2A** obtained in the Stevens rearrangement was established by single-crystal X-ray structure analysis (Figure 1). The aromatic rings are

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[4] Heterophanes are [2.2]cyclophanes that contain at least one heterocyclic ring system. In cyclophane nomenclature, [*m.n*] refers to the number of atoms in the bridge between the two ring systems. The sites of substitution on the heterocycle are denoted in parentheses; see: (a) Paudler, W. W.; Bezoari, M. D. Synthesis and Properties of Heterophanes. In: *Cyclophanes*; Keehn, P. M., Rosenfeld, S. M., Eds.; Academic Press: New York, 1983; Vol. 2. (b) Vögtle, F.; Pawlitzki, G.; Hahn, U. *Mod. Cyclophane Chem.* **2004**, 41−80.

[5] (a) Bruhin, J.; Jenny, W. *Tetrahedron Lett.* **1973**, 1215−1218. (b) Boekelheide, V.; Reingold, I. D.; Tuttle, M. *J. Chem. Soc., Chem. Commun.* **1973**, 406−407.

[6] In this paper, the heterophanes are [*m.n*]*para*-(1,3)-cyclophanes and [*m.n.*]*meta*-(1,3)-cyclophanes. The (1,3) indicates the point of substitution on the heterocycle (as ref 4a).

[7] Thomson, T.; Stevens, T. S. *J. Chem. Soc.* **1932**, 69−73.

[8] Sulfonium intermediates by alkylation/Stevens rearrangement in hydrocarbon cyclophanes: Mitchell, R. H.; Boekelheide, V. *J. Am. Chem. Soc.* **1974**, *96*, 1547−1557.

[9] (a) Ando, W.; Yagihara, T.; Tozune, S.; Migita, T. *J. Am. Chem. Soc.* **1969**, *91*, 2786−7. (b) Ando, W. *Acc. Chem. Res.* **1977**, *10*, 179−85.

[10] (a) Vedejs, E.; Hagen, J. P. *J. Am. Chem. Soc.* **1975**, *97*, 6878−80. (b) Vedejs, E. *Acc. Chem. Res.* **1984**, *17*, 358−64.

[11] The Stevens rearrangement was also carried out in the imidazolidinone series (see ref 3), providing the corresponding cyclophane in 37% yield. In this case, carbene insertion occurred into the *N,S*-acetal.

[12] The isolation of the bissulfonium ylide suggests that both ylide formation steps are much faster than the [1,2] Stevens rearrangement. The byproducts (15% determined by crude ^1H NMR against the internal standard), assumed to emanate from a single Stevens rearrangement, could not be purified away from the major product **2A** (chromatography or fractional crystallization). See 13b for a discussion of other possible products.

[13] (a) Staab, H. A.; Wahl, P.; Kay, K. Y. *Chem. Ber.* **1987**, *120*, 541−549. (b) Otsubo, T.; Kitasawa, M.; Misumi, S. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1515−1520. (c) Matsuoka, T.; Negi, T.; Otsubo, T.; Sakata, Y.; Misumi, S. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 1825−1833.

[14] Two ester conformations were found in the unit cell. X-ray diffraction data were collected on a Bruker 1K CCD diffractometer with Mo Kα (λ = 0.71073 Å) radiation using a colorless crystal with the dimensions of 0.40 × 0.13 × 0.13 mm^3. Intensity data were integrated with the SAINTPLUS program. The crystal structure was solved by direct methods with SHELXS and refined by the full-matrix least-squares method with SHELXTL. Non-hydrogen atoms were refined anisotropically, except for the atoms of the disordered groups and the solvent, which were refined isotropically. Positions of hydrogen atoms were calculated geometrically. Subsequently, H-atoms were refined as ideal CH_3 groups with $U_{iso} = 1.5U_{equiv}$ of the connected non-hydrogen atom. The remaining hydrogens were refined using the "riding" model with $U_{iso} = 1.2U_{equiv}$. One of the ethyl groups was disordered over two positions with populations refined to 63/37%. Crystal data for **2A**: $C_{31.18}H_{36.37}N_2O_9S_2Cl_{0.37}$, $M = 660.45$, triclinic, space group $P\bar{1}$, $a = 14.255(1)$ Å, $b = 14.364(1)$ Å, $c = 17.561(2)$ Å, $V = 3163.7(5)$ Å^3, $Z = 4$, $T = 90(1)$ K, $D_c = 1.387$ g cm^{-3}, $2\theta_{max} = 50.0°$, $R(F) = 8.7\%$ for 8311 reflections with $F_o > 2\sigma(F_o)$ and $R_w(F^2) = 0.24$ for all 10 956 independent reflections, 802 parameters. GOF(F^2) = 1.045.

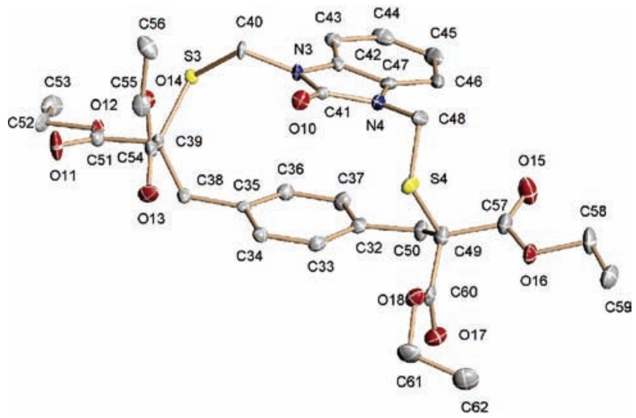
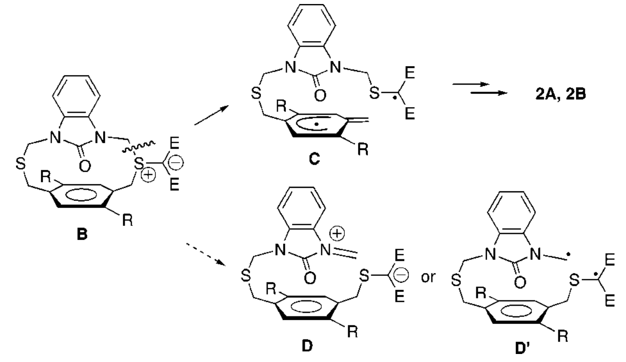


Figure 1. ORTEP drawing of [4.4]heterophane **2A** based on X-ray structure determination. The major conformer is shown. Thermal ellipsoids drawn at 50% probability.[14]

separated by a distance of 3.428 Å with the two rings roughly parallel, with their mean root square planes differing by 10.5 °C (for the major conformer). The ORTEP drawing illustrates several features that indicate transannular interaction: (1) the benzimidazolone ring is distorted from planarity; (2) the urea carbonyl is displaced from the mean heterocyclic plane (C10 is displaced by 0.062 Å and O1 is displaced by 0.186 Å from planarity). The structure also corroborates the regioselective nature of both insertions.

The regioselectivity of insertion is dictated by the stability of reactive intermediates (Scheme 3). There is evidence supporting diradical intermediates in the rearrangement of $R_2S^+C^-(CO_2R')_2$ when the migrating group R is a hydrocarbon.[15] The intermediacy of diradical **C** is consistent with this precedent, illustrating benzyl group migration (top pathway, Scheme 3). A second migration would produce cyclophanes **2A** and **2B**. However, in related systems, *N*-acyl iminium ions have been invoked in Stevens rearrangements of sulfonium ylides derived from *N*,*S*-acetals.[16] This would lead to an alternate regiochemistry of bond insertion giving plausible intermediates **D** or **D′**. The observed products **2** suggest that the top pathway predominates. It is possible that stabilization of the incipient α-radical by the nitrogen lone pair (as **D′**, lower pathway) is impaired by ground-state resonance in the benzimidazolone heterocycle.

Scheme 3. Regioselective Opening of Sulfonium Ylide



Similarly, the structure of the [3.3]cyclophane **3A** was unambiguously established by X-ray crystal structure analysis (Figure 2). The structure shows evidence of ring strain. The [3.3]cyclophane positions the urea carbonyl group directly over the benzene ring at a distance of 2.96 Å. The heterocyclic ring and the benzene ring are almost parallel, with their mean planes offset by 9.6°. Ring strain is manifested in the benzene ring where it is distorted into a boatlike conformation (the C1 and C4 carbons are elevated 0.085 Å from the ring plane). The transannular strain is apparent in the *ansa*-bridging methylenes (C7−C9; C17−C19) where the bond angles are all greater than 115°, which is a large value for sp^3-hybridized carbon atoms.

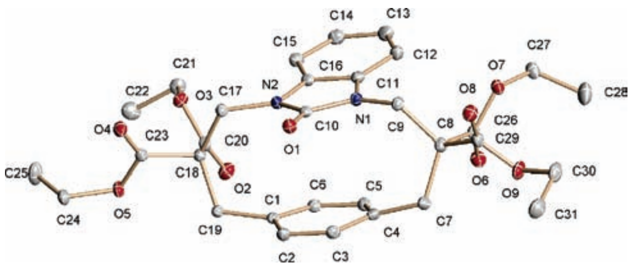


Figure 2. ORTEP drawing of [3.3]heterophane **3A** based on X-ray structure determination. Thermal ellipsoids drawn at 50% probability.[17]

The macrocyclative cyclophane ring synthesis was employed to make dithia[3.3]*meta*-(1,3)-heterophanes (Scheme 4). These novel structures feature meta substitution on the aromatic ring. Despite the anticipated ring strain of the macrocycles, the imidazolidinones **7** were readily formed under acid-catalyzed transacetalization. The benzimidazolones **8A** and **8B** were also formed in the transacetalization using 2−4 equiv of BF_3-OEt_2 which both served as a Lewis

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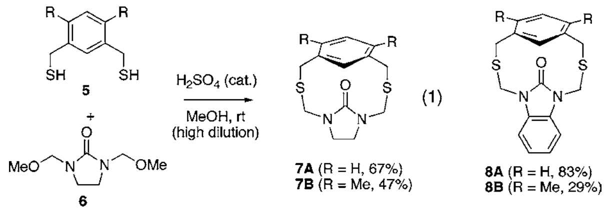
[15] (a) Schoellkopf, U.; Ostermann, G.; Schossig, J. *Tetrahedron Lett.* **1969**, 2619−22. (b) Baldwin, J. E.; Erickson, W. F.; Hackler, R. E.; Scott, R. M. *J. Chem. Soc., Chem. Commun.* **1970**, 576−578. (c) Ando, W.; Yamada, M.; Matsuzaki, E.; Migita, T. *J. Org. Chem.* **1972**, *37*, 3791−3797.

[16] X-ray diffraction data were collected on a Bruker 1K CCD diffractometer with Mo Kα (λ = 0.71073 Å) radiation using a colorless crystal with the dimensions of 0.30 × 0.2 × 0.1 mm^3. Intensity data and refinement as for structure **2A** (see also the cif file in Supporting Information). Crystal data for **3A**: $C_{31}H_{36}N_2O_9$, $M = 580.62$, triclinic, space group P$\bar{1}$, $a = 9.5255(3)$ Å, $b = 10.5137(3)$ Å, $c = 16.1411(7)$ Å, $V = 1415.47(9)$ Å^3, $Z = 2$, $T = 90(2)$ K, $D_c = 1.362$ g cm^{-3}, $2\theta_{max} = 60.0°$, $R(F) = 3.98\%$ for 6558 reflections with $F_o > 2\sigma(F_o)$ and $R_w(F^2) = 0.1096$ for all 22 670 independent reflections, 384 parameters. GOF(F^2) = 1.023.

[17] (a) Kametani, T.; Kawamura, K.; Akagi, T.; Fujita, C.; Honda, T. *Heterocycles* **1988**, *27*, 2531−2534. (b) Kametani, T.; Yukawa, H.; Honda, T. *J. Chem. Soc., Perkin 1* **1990**, 571−577. (c) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*; Wiley: New York, 1998; pp 371−373. (d) Prasad, K.; Kneussel, P.; Schulz, G.; Stuetz, P. *Tetrahedron Lett.* **1982**, *23*, 1247−1250.

Scheme 4. Novel *meta*-Heterophanes

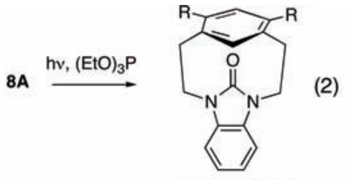


acid catalyst and sequestered the methanol formed as a byproduct. In both cases, the dimethyl substitution proved detrimental and resulted in lower chemical yields (**7B** vs **7A**; **8B** vs **8A**).

The strained dithia[3.3]*meta*-cyclophanes did not undergo Stevens rearrangement. Cyclophanes **7** and **8** were subjected to Stevens rearrangement under standard high dilution conditions used to prepare the cyclophanes in Scheme 1. Under these conditions, no tractable products were obtained and the Stevens ring expansion products were not observed. This was surprising. Structural distortion in this cyclophane may decrease the orbital overlap needed for the fragmentation of the sulfonium ylide intermediates. It is also possible that the greater ring strain of the dithia[3.3]*meta*-cyclophane[18] triggers ring opening of the formed sulfonium ylide, which results in separation of the reactive intermediate (ion pair or radical pair) and leads to polymerization.

Because the dithia[4.4]*meta*-(1,3)heterophanes could not be accessed by Stevens rearrangement, we examined whether the *meta*-heterophanes would undergo photochemical sulfur atom extrusion. This would gain access to the [2.2]*meta*-(1,3)heterophane. The dithia[3.3]benzimidazolone cyclophane **8A** was irradiated in $(EtO)_3P$ solvent to provide the novel [2.2]*meta*-cyclophane **9A** in 25% yield (eq 2).

The structure of the [2.2]*meta*-cyclophane **9A** is illustrated in Figure 3. The anti conformation was observed with the meta proton of the benzene ring (H_a) positioned 2.75 Å above the heterocycle. A strong shielding of the single meta proton H_a by the heterocycle was observed (5.2 vs 7.08 ppm for the dithia[4.4]heterophane precursor **8A**).[19] The crystal structure also shows deformation of the C7 and C16 methylene groups attached to the urea nitrogen atoms. For example, the C7 group is twisted 30.22° out of the ideal planar conformation of the urea ($C_7N_2C_{17}O_1$ torsion angle). Evidence of this distortion can also be found in solution. In the C13 spectrum, deshielding of the urea carbonyl was noted (158.2 ppm for **9A** vs 153.6 ppm for **8A**). This deshielding is attributed to out-of-plane bending (C7 and C16; see ORTEP in Figure 3), which precludes optimal orbital overlap through amide resonance. Last, the C8 and C15 carbons attached to the meta-substituted benzene ring show elevation from the aromatic plane by 26.75° and 26.42°, respectively. This deformation from ideal sp^2 geometry is greater than the observed distortion in the [2.2]*para*-imidazolone cyclophanes reported previously.[3]



9A (R = H, 25%)

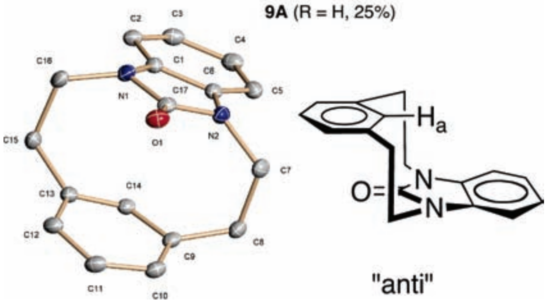


Figure 3. ORTEP drawing of *meta*-cyclophane **9A** based on X-ray structure determination. Thermal ellipsoids drawn at 50% probability.[20]

In conclusion, we have demonstrated that a double Stevens rearrangement can be used to expand sulfur-containing heterophanes. Future studies are focused on the conversion of the urea-containing heterophanes into their respective N-heterocyclic carbenes.

Acknowledgment. The authors thank Prof. Philip Coppens for use of his X-ray diffractometer, Dr. Cara Nygren for assistance with the crystallographic data, Prof. F. G. West (U. Alberta) for helpful suggestions, and Prof. H. M. L. Davies for a gift of Rh_2OAc_4. The authors gratefully acknowledge the NSF (Career CHE-092434) for support of this work.

Supporting Information Available: Detailed experimental procedures and characterization data for new compounds and cif files for **2A**, **3A**, and **9A**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[18] Calculations on the hydrocarbon [2.2]*metapara*-cyclophane estimate ring strain at 18.90 kcal/mol: Caramori, G. F.; Galembeck, S. E.; Laali, K. K. *J. Org. Chem.* **2005**, *70*, 3242−3250.

[19] For a discussion on ^{1}H NMR in cyclophanes, see: Pascal, R. A., Jr. *Eur. J. Org. Chem.* **2004**, 3763−3771.

[20] X-ray diffraction data were collected on a Bruker 1K CCD diffractometer with Mo Kα ($\lambda = 0.71073$ Å) radiation using a colorless crystal with the dimensions of $0.43 \times 0.30 \times 0.13$ mm^3. Intensity data and refinement as for structure **2A** (see also the cif file in the Supporting Information). Crystal data for **9A**: $C_{17}H_{10}N_2O$, $M = 264.32$, orthorhombic, space group Pbca, $a = 8.1780(3)$ Å, $b = 12.3849(4)$ Å, $c = 25.8621(9)$ Å, $V = 2619.41(16)$ Å^3, $Z = 8$, $T = 90(2)$ K, $D_c = 1.340$ g cm^{-3}, $2\theta_{max} = 68.6°$, $R(F) = 3.71\%$ for 4231 reflections with $F_o > 2\sigma(F_o)$ and $R_w(F^2) = 0.1106$ for all 51 763 independent reflections, 384 parameters. GOF(F^2) = 1.034.