Supramolecular Chemistry

DOI: 10.1002/anie.200901200

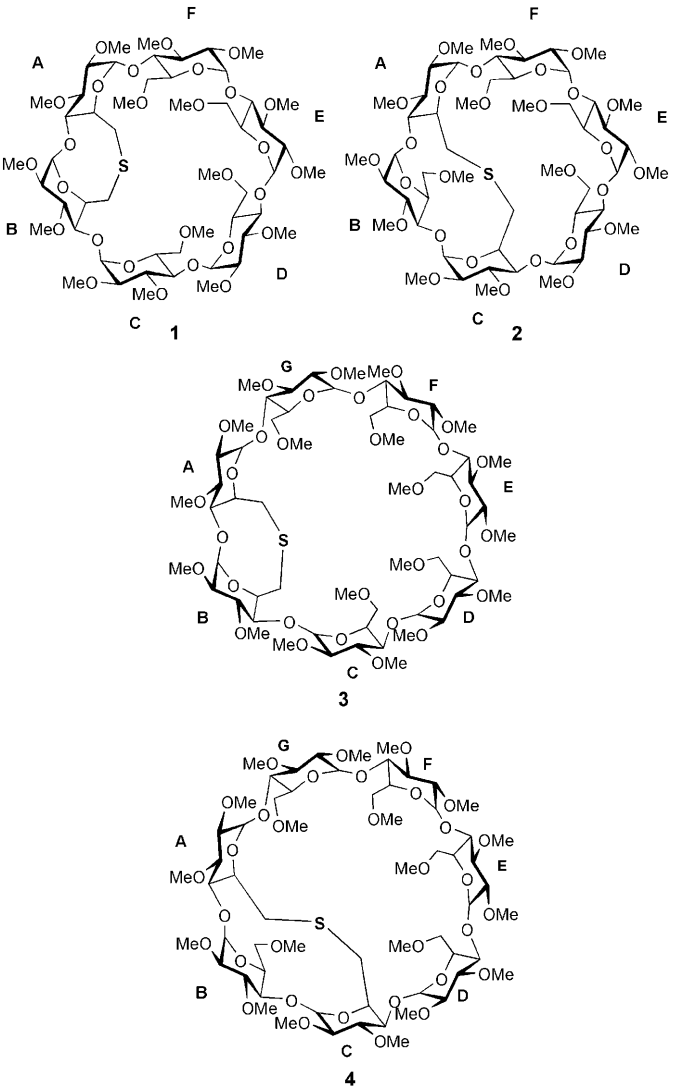
Self-Mediated Stereoselective Oxidation of Thia-Capped Cyclodextrins**

Dominique Armspach, Dominique Matt,* and Loic Toupet*

The timeless fascination with the natural cyclodextrins (CDs) largely arises from their chiral, toruslike structure and their ability to complex a wide range of molecules within their cavity.[1–6] An important concern for CD chemistry is their chemical modification.[7–12] Tailoring CDs, which is usually achieved by anchoring appropriate functional groups at the alcoholic oxygen atoms, makes it possible to access new receptors to meet specific requirements of the targeted host–guest systems.

Although CDs are commonly used as efficient templates in organic synthesis, by allowing reactions to take place within their annulus, their receptor properties have been rarely exploited for their own modification.[13] Striking examples of self-mediated, selective CD transformations include the regioselective monofunctionalization of β-CD with arylsulfonates in basic media,[14] and the regioselective cycloaddition of alkyne- or alcene-substituted β-CDs with nitrile oxides.[15,16] Herein we present a unique example of stereoselective cyclodextrin transformation, namely the oxidation of CD thioethers into *endo* (*S*)-sulfoxides,[17] in which the CD cavity exerts supramolecular control over the reaction stereoselectivity. The chemistry of sulfoxides is currently an active research area.[18,19] Sulfoxides constitute valuable tools in preparative organic chemistry, in which they are mainly employed as auxiliaries in asymmetric synthesis[20–24] or as chiral ligands for metal-catalyzed reactions.[25] A number of sulfoxides also display biological activity, some of which have important applications in medicinal chemistry.[26,27] To date, chiral RR′S=O groups have not been associated in a covalent manner with a cyclodextrin unit, however CDs have been used as mediators for the synthesis of chiral sulfoxides.[13,28,29]

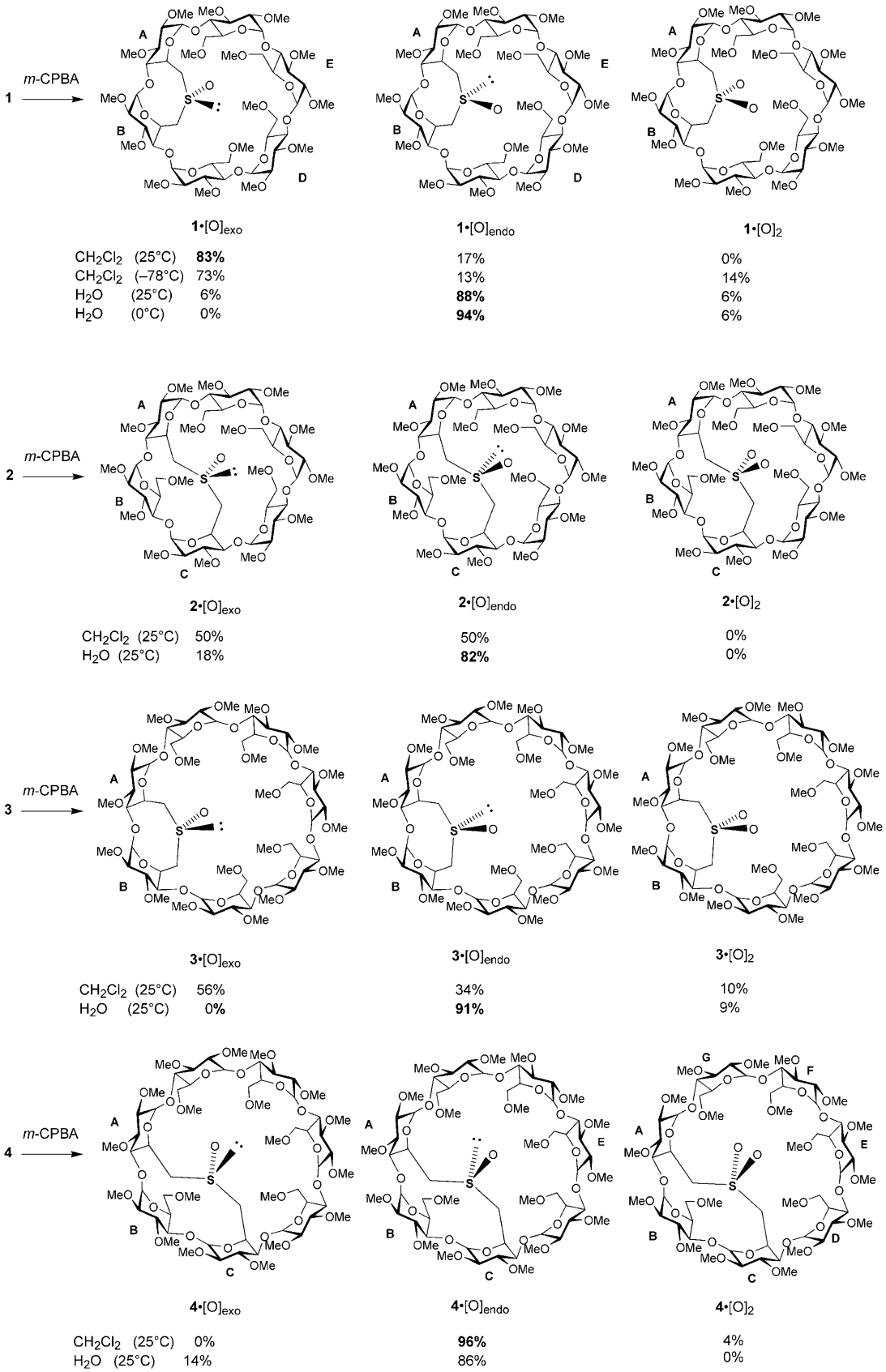
The oxidation reactions were performed on the sulfur thia-capped, permethylated CDs **1**–**4**, which are all comprised of a prochiral sulfur atom possessing both an *endo*- and an *exo*-oriented lone pair of electrons. Selective mono-oxidation was ensured by using *m*-chloroperoxybenzoic acid (*m*-CPBA) in a 1:1 acid/CD stoichiometry; higher proportions of the oxidant led to the corresponding sulfone. Notably, all the sulfoxides are water soluble. The distinction between *exo* and *endo* products was achieved by means of X-ray diffraction studies.[30] Each diastereoisomer can in practice be identified unambiguously by ^{1}H NMR analysis; the spectra of the *endo*-oxidation products (**1**·$[O]_{endo}$, **2**·$[O]_{endo}$, **3**·$[O]_{endo}$, **4**·$[O]_{endo}$; Scheme 1) show specific H5 proton signals significantly low-field shifted with respect to those of the *exo* products as well as to those of the starting sulfides (see the Supporting Information). The same observation holds for some H6 protons of the A and B units of the *exo*-products **1**·$[O]_{exo}$ and **3**·$[O]_{exo}$.



[*] Dr. D. Armspach, Dr. D. Matt
Laboratoire de Chimie Inorganique Moléculaire et Catalyse
Institut de Chimie UMR 7177 CNRS, Université de Strasbourg
67008 Strasbourg Cedex (France)
E-mail: darmspach@chimie.u-strasbg.fr
dmatt@chimie.u-strasbg.fr
Dr. L. Toupet
Groupe Matière Condensée et Matériaux, UMR 6626 CNRS,
Université de Rennes 1, 35042 Rennes Cedex (France)

[**] We thank the Agence Nationale de la Recherche for support (ANR Watercat).

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200901200.



Scheme 1. Comparison of the oxidation reactions of **1**–**4** in both CH_2Cl_2 and H_2O.

We anticipated that the cavity would, by steric considerations, protect the *endo* lone pair of electrons of each sulfide, and therefore possibly direct the oxidation process. We first examined oxidation reactions in dichloromethane (Scheme 1) and found that α-, and to a lesser extent, β-CDs having AB linking units induced relatively high selectivities for *exo* oxidation (e.g., *exo*/*endo* = 83:17 for the oxidation of **1**). This finding is consistent with the fact that in the solid state the AB-bridged sulfoxide **1**·$[O]_{endo}$ has a sterically unencumbered *exo* lone pair of electrons (Figure 1). In contrast,

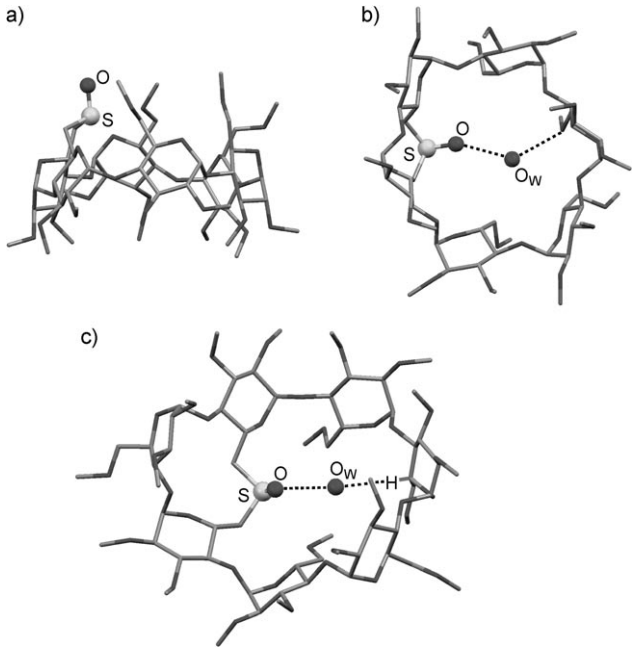


Figure 1. Side view of **1**·$[O]_{exo}$ (a) and bottom views of **1**·$[O]_{endo}$ (b) and **4**·$[O]_{endo}$ (c) in the solid state (hexane guests not shown). Both sulfoxides **1**·$[O]_{endo}$ and **4**·$[O]_{endo}$ contain a water molecule ($SO\cdots O_w$ = 2.77 Å and 2.73 Å, respectively). Other included solvent molecules are not shown. Note that glucose ring B of **4**·$[O]_{endo}$ adopts a $^1H_2$ half-chair conformation. All other glucose rings in each of the three structures above are in the standard $^4C_1$ conformation.[31,32]

whereas the α-CD with an AC link (**2**) showed no selectivity at all, the β-CD analogue **4** led exclusively to the *endo* product. Notably, in the latter case small amounts of sulfone were detected, but its formation could be prevented by using benzene as the solvent. The high *endo* selectivity observed with **4** versus **2** is best rationalized in terms of steric crowding about the *exo* lone pair of electrons of **4**. This steric crowding was confirmed by examining the X-ray crystallographic structures of **4**[30] and **4**·$[O]_{endo}$ (Figure 1) in which two methoxy groups are in close contact with the *exo*-oriented portion of the sulfur atom, which is unlike the situation found in **3**. Therefore, simple steric considerations may explain the observed selectivities in organic media.

Methylated α- and β-CDs display good receptor properties in water towards aromatic compounds.[33] We therefore wondered whether the oxidation using *m*-CPBA in this medium would favor selective formation of an *endo*-sulfoxide product. In all cases, carrying out the oxidation at 25 °C resulted in the expected *endo* product with remarkably high selectivity (*de* values up to 100 %; Scheme 1). We found that *endo* oxidation of the smaller α-CDs was significantly improved when operating near 0 °C. We also noted that under optimal reaction conditions the *exo*-sulfoxide product was not produced, but small amounts of sulfone were found. A logical explanation for this reversal of selectivity is the formation of a supramolecular CD⊃*m*-CPBA host–guest complex in water, which promotes a very fast intracavity oxidation. The addition of 20 equivalents of *m*-chlorobenzoic acid, a potential inhibitor which is structurally related to *m*-CPBA, did not significantly affect the efficiency of the *endo*-oxidation process. Interestingly, the strongly distorted AC thia-capped CDs **2** and **4** led to somewhat less selective oxidations with respect to the AB counterparts, which maintained the usual circular shape.[34] This result likely reflects the poorer receptor properties of the former towards aromatic guest molecules, notably *m*-CPBA. Remarkably, the inclusion of a strongly bound water molecule was observed for the *endo*-sulfoxide products **1**·$[O]_{endo}$ and **4**·$[O]_{endo}$.[35] In both cases the water molecule is hydrogen bonded to the *endo*-oriented S=O group ($O\cdots O_w$ = 2.77 Å in **1**·$[O]_{endo}$; 2.73 Å in **4**·$[O]_{endo}$), as well as to another inner cavity atom (6-OMe^E atom of **1**·$[O]_{endo}$; $H5^F$ in **4**·$[O]_{endo}$).

Overall, we have synthesized the first cyclodextrins having embedded chiral sulfoxides. Their syntheses, which are highly stereoselective, rely on the facile formation of a CD⊃oxidant inclusion complex in aqueous medium, which drives the reaction towards the *endo* product. This process is a solvent-controlled process, as demonstrated by the fact that the same reaction leads to sulfoxides having the opposite configuration when carried out in an organic solvent. It may be anticipated that the *endo*-sulfoxide products may have the ability to form multipoint hydrogen bonds with appropriate guests within their cavity, which will open the way to new applications in asymmetric synthesis, separation science, and molecular recognition in aqueous media.

Experimental Section

Full experimental details including X-ray structural data are given in the Supporting Information. CCDC 621588, 621591 and 621590 contain the supplementary crystallographic data for **1**·$[O]_{exo}$, **1**·$[O]_{endo}$, and **4**·$[O]_{endo}$, respectively. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Received: March 3, 2009
Published online: May 14, 2009

Keywords: cyclodextrins · oxidation · stereoselectivity · sulfoxides · supramolecular chemistry

[1] G. Wenz, *Angew. Chem.* **1994**, *106*, 851 – 870; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 803 – 822.
[2] R. Breslow, *Acc. Chem. Res.* **1995**, *28*, 146 – 153.
[3] J. Szejtli, *Chem. Rev.* **1998**, *98*, 1743 – 1754.
[4] W. Saenger, J. Jacob, K. Gessler, T. Steiner, D. Hoffmann, H. Sanbe, K. Koizumi, S. M. Smith, T. Takaha, *Chem. Rev.* **1998**, *98*, 1787 – 1802.

[5] E. Engeldinger, D. Armspach, D. Matt, *Chem. Rev.* **2003**, *103*, 4147 – 4174.
[6] R. Villalonga, R. Cao, A. Fragoso, *Chem. Rev.* **2007**, *107*, 3088 – 3116.
[7] A. R. Khan, P. Forgo, K. J. Stine, V. T. D'Souza, *Chem. Rev.* **1998**, *98*, 1977 – 1996.
[8] D. Armspach, D. Matt, *Carbohydr. Res.* **1998**, *310*, 129 – 133.
[9] C. J. Easton, S. F. Lincoln, *Modified Cyclodextrins: Scaffolds and Templates for Supramolecular Chemistry*, Imperial College Press, London, **1999**.
[10] A. J. Pearce, P. Sinaÿ, *Angew. Chem.* **2000**, *112*, 3756 – 3758; *Angew. Chem. Int. Ed.* **2000**, *39*, 3610 – 3612.
[11] D.-Q. Yuan, Y. Kitagawa, K. Aoyama, T. Douke, M. Fukudome, K. Fujita, *Angew. Chem.* **2007**, *119*, 5112 – 5115; *Angew. Chem. Int. Ed.* **2007**, *46*, 5024 – 5027.
[12] M. Sollogoub, *Eur. J. Org. Chem.* **2009**, 1295 – 1303.
[13] K. Takahashi, *Chem. Rev.* **1998**, *98*, 2013 – 2034.
[14] A. Ueno, R. Breslow, *Tetrahedron Lett.* **1982**, *23*, 3451 – 3454.
[15] A. G. Meyer, C. J. Easton, S. F. Lincoln, G. W. Simpson, *Chem. Commun.* **1997**, 1517 – 1518.
[16] C. J. Easton, *Pure Appl. Chem.* **2005**, *77*, 1865 – 1871.
[17] The stereochemistry of the pseudo-chiral sulfur atoms was assigned by giving arbitrarily priority to glucose unit A over glucose units B or C.
[18] D. Madec, F. Mingoia, C. Macovei, G. Maitro, G. Giambastiani, G. Poli, *Eur. J. Org. Chem.* **2005**, 552 – 557.
[19] J.-P. Goddard, C. Gomez, F. Brebion, S. Beauvière, L. Fensterbank, M. Malacria, *Chem. Commun.* **2007**, 2929 – 2931.
[20] G. Solladié, *Synthesis* **1981**, 185 – 196.
[21] G. Solladié, *Pure Appl. Chem.* **1988**, *60*, 1699 – 1704.
[22] G. H. Posner, *Acc. Chem. Res.* **1987**, *20*, 72 – 78.
[23] I. Fernández, N. Khiar, *Chem. Rev.* **2003**, *103*, 3651 – 3706.
[24] C. Carreño, G. Hernández-Torres, A. Urbano, F. Colobert, *Eur. J. Org. Chem.* **2008**, 2035 – 2038.
[25] K. Watanabe, T. Hirasawa, K. Hiroi, *Chem. Pharm. Bull.* **2002**, *50*, 372 – 379.
[26] G. Mestroni, E. Alessio, G. Sava, S. Pacor, M. Coluccia, A. Boccarelli, *Met.-Based Drugs* **1994**, *1*, 41 – 63.
[27] M. C. Carreño, *Chem. Rev.* **1995**, *95*, 1717 – 1760.
[28] H. Sakuraba, K. Natori, Y. Tanaka, *J. Org. Chem.* **1991**, *56*, 4124 – 4129.
[29] M. Bonchio, T. Carofiglio, F. Di Furia, R. Fornasier, *J. Org. Chem.* **1995**, *60*, 5986 – 5988.
[30] X-ray crystallogrpahic structures were obtained for **4**, **1**·$[O]_{exo}$, **1**·$[O]_{endo}$, **2**·$[O]_{endo}$, **2**·$[O]_{exo}$, **4**·$[O]_{endo}$. Only those of **1**·$[O]_{exo}$, **1**·$[O]_{endo}$, and **4**·$[O]_{endo}$ are reported herein.
[31] D. Cremer, J. A. Pople, *J. Am. Chem. Soc.* **1975**, *97*, 1354 – 1358.
[32] IUPAC-IUB Joint Commission on Biochemical Nomenclature (JCBN). Conformational nomenclature for five- and six-membered ring forms of monosaccharides and their derivatives (Recommendations 1980). *Pure Appl. Chem.* **1981**, 53, 1901 – 1905.
[33] M. V. Rekharsky, Y. Inoue, *Chem. Rev.* **1998**, *98*, 1875 – 1917.
[34] The anomeric signals in the ^{1}H NMR spectra of the distorted AC thia-capped CDs **2** and **4** are spread out over a range of $\delta = 0.80$ ppm and $\delta = 0.87$ ppm, respectively, whereas those of circular shaped AB- thia-capped CDs **1** and **3** resonate within much narrower windows ($\delta = 0.07$ ppm and $\delta = 0.23$ ppm, respectively).
[35] No such noncovalent bonds were found with the *exo*-sulfoxide products.

