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ORIGINAL ARTICLE

# NMR study of host–guest complexes of disulfonated derivatives of 9, 10-diphenylanthracene and corresponding endoperoxides with cyclodextrins

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**Abstract** Disulfonated derivatives of 9,10-diphenyl anthracene (dsDPA) are known carriers of singlet oxygen. DsDPA and corresponding endoperoxides ($dsDPAO_2$) form host–guest complexes with native cyclodextrins (i.e. $\beta$-CD and $\gamma$-CD). The modes of host–guest interaction were studied by $^1$H NMR and 2D-NMR (ROESY). Specific inclusions of phenyl groups of dsDPA/$dsDPAO_2$ into the cyclodextrin cavities were found for both $\beta$-CD and $\gamma$-CD. The mode of interaction depends on the size of the CD cavity and the position of the sulfonate group.

**Keywords** Anthracene derivatives · Cyclodextrin · Endoperoxides · Host–guest complexes · NMR

Dedicated to the memory of Jan Sejbal.

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## Introduction

Cyclodextrins (CDs) are cyclic non-reductive oligosaccharides formed by six or more units of α-D-glucopyranose bonded through α-(1 → 4) bonds. The most common types of CDs are α-, $\beta$- and $\gamma$-CD composed of 6, 7 and 8 such units, respectively (Fig. 1). Tertiary structures of CDs can be described as a hollow truncated cone. The interior, lined with C–H bonds and glycosidic oxygen bridges, is hydrophobic while the exterior is hydrophilic due to hydroxyl groups [1, 2].

Consequently, CDs are water-soluble and form inclusion host–guest complexes with a variety of guest organic or inorganic molecules [1–3]. Cyclodextrins are studied primarily as carriers of drugs [4–6]. Supramolecular complexes with CDs frequently improve the resistance of host molecules to thermal degradation and increase their solubility, biological activity and availability.

The formation of the host–guest or other type supramolecular complexes with CDs can be observed by NMR spectroscopy which represents one of the most powerful tools for describing complex formation in solution [7]. Information provided by $^1$H NMR technique includes the confirmation of complex formation, calculation of the stoichiometry and stability constant and definition of geometry of the complex, e.g. the orientation of the guest molecule in the CD cavity [8–11]. The method is based on observation of chemical shift differences in the presence and absence of guest molecules [11–12].

More detailed insight of the geometry of supramolecular complex can be obtained by the application of 2D-NMR advanced techniques, implementing intermolecular nuclear Overhauser effects (NOEs), e.g. 2D-NOESY and 2D-ROESY. NOE cross-peaks may be observed between spatially close protons (internuclear distances smaller than 3–5 Å)

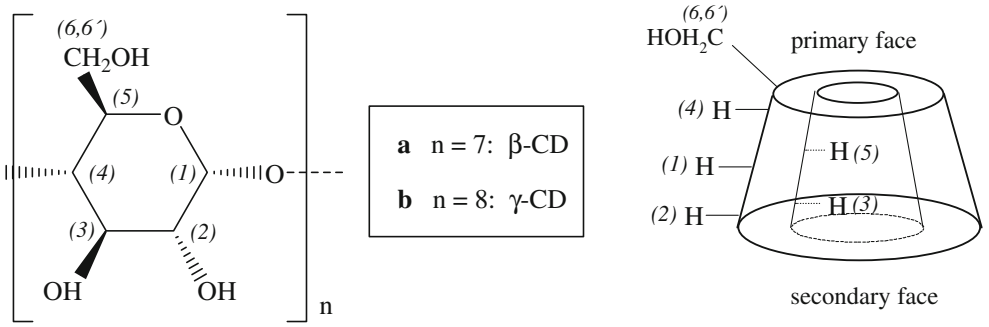



**Fig. 1** The schematic structure of CDs. Positions of hydrogen atoms inside and outside CD cavity

and provide useful information about the structure of the supramolecular system in solution [7, 13, 14]. 2D-ROESY (Rotating frame Spectroscopy) is more suitable for determination of spatial arrangement of medium size molecules in solution [11, 13–17]. This technique allows to circumvent the problem of extremely small NOE's resulting from the unfavorable correlation times of supramolecular complexes with a relative molecular weight around 1,000.

In our previous study [18] we described the preparation of water-soluble singlet oxygen ($^1O_2$) acceptors disodium salt of 2,7-disulfonato-9,10-diphenylanthracene (2,7-dsDPA, **1**), 2,6-disulfonato-9,10-diphenylanthracene (2,6-dsDPA, **2**) and corresponding endoperoxides (2,7-dsDPAO$_2$, **3** and 2,6-dsDPAO$_2$, **4**) prepared by interaction **1** and **2** with $^1O_2$. Singlet oxygen was generated via photosensitized reaction. Structures of compounds **1**–**4** are shown in the Scheme 1. We studied the complexation of compounds **1** and **2** with $\beta$-CD and $\gamma$-CD by spectrophotometric methods and we determined the stoichiometry and binding constants $K_b$ (see Table 1) [18]. We found out that formation of inclusion complexes of **1**–**4** with CDs influences some photochemical and physiochemical properties of molecules **1**–**4**. Aromatic endoperoxides **3** and **4** can be used as secondary sources of $^1O_2$ via thermal decomposition.

In the current study we prepared endoperoxides **3** and **4** by [4 + 2] cycloaddition **1** and **2** with $^1O_2$ generated via chemical reaction and we studied inclusion complexes of **1**–**4** with $\beta$-CD and $\gamma$-CD. Interaction of endoperoxides **3** and **4** with CDs can not be observed by UV–Vis nor fluorescence spectroscopy due to absence of suitable absorption or emission bands. We concerned our attention to reveal the detailed geometry of the inclusion complexes of **1**–**4** with CDs and to compare the complexation modes of endoperoxides **3** and **4** and the parent anthracene derivatives **1** and **2** with CDs using $^1$H NMR and 2D NMR methods.

## Materials and methods

### General comments

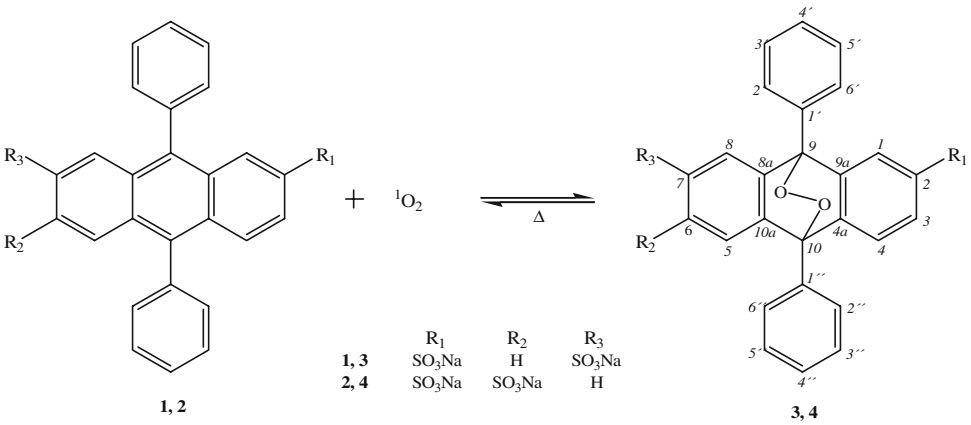
All NMR spectra were performed on a Varian–Inova 400 MHz spectrometer using a 5 mm gradient inverse

**Table 1** Stoichiometry and binding constants $K_b$ of complexes of **1** and **2** with native $\beta$- and $\gamma$-CD calculated using binding isotherm analysis [18]

| System | Stoichiometry | $K_b$ ($M^{-1}$) |
|---|---|---|
| **1**:$\beta$-CD | 1:1 | $1.4 \times 10^2$ |
| **1**:$\gamma$-CD | 1:1 | $1.2 \times 10^2$ |
| **2**:$\beta$-CD | –[a] | –[a] |
| **2**:$\gamma$-CD | 1:1 | $2.6 \times 10^3$ |

[a] No spectral evidence of complex formation

**Scheme 1** Structure and numbering schema of compounds **1**, **2** and **3, 4**



probe and/or 5 mm broadband probe. Frequency of $^{1}H$ nuclei were 399.951 MHz and frequency of $^{13}C$ nuclei were 100.579 MHz. All samples were measured in $D_2O$ using 2-methylpropan-2-ol as an internal reference ($^{1}H$ NMR $\delta$ 1.25 ppm and $^{13}C$ NMR $\delta$ 31.6 ppm) at 308 K. Chemical shift values $\delta$ are reported in parts per million and coupling constants $J$ are in hertz. Two-dimensional ROESY experiments were recorded using a standard pulse sequence with the mixing time set to a short value (100 ms) to ensure that cross-peaks originated from NOE only. The 2D-NOESY spectra were measured with 300 ms mixing time.

## Synthesis of compounds **1** and **2**

All chemicals were purchased from Aldrich.

Synthesis of compounds **1** and **2** was based on sulfonation of 9,10-diphenylanthracene with oleum [18, 19]. Products were identified by NMR spectroscopy. The proton and carbon signals were determined by $^{1}H$, $^{13}C$, DEPT and 2D-NMR (COSY, gHSQC, gHMBC and NOESY).

### *Sodium 9,10-diphenylanthracene-2,7-disulfonate (2,7-dsDPA, **1**)*

Yellow crystals, $^{1}H$ NMR $\delta$ 8.21 (2H, d, $J = 1.4$ Hz, H-1, H-8), 7.85 (2H, d, $J = 9.2$ Hz, H-4, H-5), 7.73 (1H, m, H-4′), 7.72 (2H, m, H-3′, H-5′), 7.70 (2H, m, H-3, H-6), 7.66 (1H, m, H-4″), 7.65 (2H, m, H-3″, H-5″), 7.51 (2H, m, H-2′, H-6′), 7.43 (2H, m, H-2″, H-6″); $^{13}C$ NMR $\delta$ 142.7 (1C, s, C-9), 141.5 (2C, s, C-2, C-7), 139.5 (1C, s, C-1″), 139.5 (1C, s, C-10), 138.7 (1C, s, C-1′), 133.1 (2C, d, C-2′, C-6′), 133.0 (2C, d, C-2″, C-6″), 132.7 (2C, s, C-4a, C-10a), 130.8 (2C, s, C-8a, C-9a), 130.8 (1C, d, C-4′), 130.7 (2C, d, C-4, C-5), 130.4 (2C, d, C-3′, C-5′), 130.4 (2C, d, C-3″, C-5″), 130.1 (1C, d, C-4″), 126.7 (2C, d, C-1, C-8), 123.9 (2C, d, C-3, C-6).

### *Sodium 9,10-diphenylanthracene-2,6-disulfonate (2,6-dsDPA, **2**)*

Yellow crystals, $^{1}H$ NMR $\delta$ 8.15 (2H, d, $J = 1.8$ Hz, H-1, H-5), 7.84 (2H, d, $J = 9.2$ Hz, H-4, H-8), 7.69 (4H, m, H-3′, H-5′), 7.68 (2H, m, H-4′), 7.67 (2H, m, H-3, H-7), 7.39 (4H, m, H-2′, H-6′); $^{13}C$ NMR $\delta$ 141.6 (2C, s, C-2, C-6), 141.1 (2C, s, C-9, C-10), 139.1 (2C, s, C-1′), 133.1 (4C, d, C-2′, C-6′), 132.1 (2C, s, C-4a, C-8a), 131.2 (2C, s, C-9a, C-10a), 130.7 (4C, d, C-3′, C-5′), 130.6 (2C, d, C-4, C-8), 130.2 (2C, d, C-4′), 126.6 (2C, d, C-1, C-5), 123.5 (2C, d, C-3, C-7).

## Preparation of compounds **3** and **4**

Compounds **3** and **4** were prepared via [4 + 2] cycloaddition with singlet oxygen $^{1}O_2$. As the chemical source of $^{1}O_2$ for chemical reactions was used $H_2O_2/MoO_4^{2-}$ system, based on $H_2O_2$ disproporcionation leading to $H_2O$ and $^{1}O_2$ [20–23]. Anion $MoO_4^{2-}$ acts in the reaction as a catalyst and as an intermediate product form diperoxomolybdenate anion $MoO_6^{2-}$:

$$2H_2O_2 + MoO_4^{2-} \leftrightarrow 2H_2O + MoO_6^{2-}$$

$$MoO_6^{2-} \leftrightarrow MoO_4^{2-} + {}^{1}O_2$$

Typical procedure: 40 mg (73.4 μmol) **1** or **2** and 0.475 g (1.96 mmol) $Na_2MoO_4$. 2 $H_2O$ were dissolved in 38 mL 0.05 M carbonate buffer (pH 10) and 7 mL 30% $H_2O_2$ was gradually added. After the addition of $H_2O_2$ the solution changes the frame through red yellow color. After 8 h the solution became colorless. The prepared endoperoxides **3** and **4** were purified by gel chromatography using $H_2O$ as mobile phase. The aqueous solutions of endoperoxides **3**, **4** were dried in vacuum and lyophilized to solid form. Chemical yields of **3** and **4** were 30 mg. The identities of endoperoxides were verified by NMR ($^{1}H$, $^{13}C$ and DEPT, COSY, gHSQC, gHMBC).

### *Endoperoxide of sodium 9,10-diphenylanthracene-2,7-disulfonate (2,7-dsDPAO$_2$, **3**)*

Yellow crystals, $^{1}H$ NMR $\delta$ 7.79 (2H, dd, $J_1 = 8.1$ Hz, $J_2 = 1.8$ Hz, H-3, H-6), 7.76(2H, m, H-2′, H-6′), 7.68–7.80 (2H, m, H-3′, H-5′), 7.68–7.80 (1H, m, H-4′) 7.67 (2H, d, $J = 1.8$ Hz, H-1, H-8), 7.61 (2H, m, H-2″, H-6″), 7.57–7.59 (2H, m, H-3″, H-5″), 7.57–7.59 (1H, m, H-4″), 7.37 (2H, d, $J = 8.1$ Hz, H-4, H-5); $^{13}C$ NMR $\delta$ 144.8 (2C, s, C-2, C-7), 143.6 (2C, s, C-4a, C-10a), 141.7 (2C, s, C-8a, C-9a), 132.9 (1C, s, C-1′), 132.7 (1C, s, C-1″), 131.3 (1C, d, C-4″) 131.1 (2C, d, C-2′, C-6′), 131.0 (1C, d, C-4′), 130.8 (2C, d, C-2″, C-6″), 128.9 (2C, d, C-3′, C-5′), 128.9 (2C, d, C-3″, C-5″), 127.7 (2C, d, C-3, C-6), 126.6 (2C, d, C-4, C-5), 122.8 (2C, d, C-1, C-8), 86.4 (1C, s, C-9), 86.2 (1C, s, C-10).

### *Endoperoxide of sodium 9,10-diphenylanthracene-2,6-disulfonate (2,6-dsDPAO$_2$, **4**)*

Yellow crystals, $^{1}H$ NMR $\delta$ 7.77 (2H, dd, $J_1 = 8.1$ Hz, $J_2 = 1.8$ Hz, H-3, H-7), 7.72 (4H, m, H-2′, H-6′), 7.72 (4H, m, H-3′, H-5′), 7.69 (2H, m, H-4′), 7.65 (2H, d, $J = 1.8$ Hz, H-1, H-5), 7.41 (2H, d, $J = 8.1$ Hz, H-4, H-8); $^{13}C$ NMR $\delta$ 144.7 (2C, s, C-2, C-6), 143.8 (2C, s, C-4a, C-8a), 141.5 (2C, s, C-9a, C-10a), 132.8 (2C, s, C-1′), 131.2 (2C, d, C-4′), 131.0 (4C, d, C-2′, C-6′), 129.0 (4C, d, C-3′, C-5′), 127.7 (2C, d, C-3, C-7), 126.6 (2C, d, C-4, C-8), 122.9 (2C, d, C-1, C-5), 86.4 (2C, s, C-9, C-10).

Preparation of host–guest complexes

Native cyclodextrins ($\beta$-CD, $\gamma$-CD, Fluka) were used as received.

We prepared samples with molar 1:2 host/guest ratio for each complex. Solutions of CDs and of compounds **1**–**4** in $D_2O$ were prepared with the help of sonication. Typical concentrations were 14.7 mmol $L^{-1}$ dsDPA/dsDPA$O_2$ with 7.4 mmol $L^{-1}$ CDs. The $^1$H NMR, $^{13}$C NMR, DEPT, gHSQC, gHMBC, COSY, NOESY and ROESY spectra were measured for all complexes with $\beta$-CD and $\gamma$-CD.

*Host–guest complex of 2,7-dsDPA (**1**) with β-CD*

*βCD:* $^1$H NMR $\delta$ 5.03 (1H, d, $J = 3.4$ Hz, H−1), 3.87 (2H, m, H-6, H-6′), 3.82 (1H, t, $J = 9.5$ Hz, H-3), 3.78 (1H, m, H-5), 3.60 (1H, dd, $J_1 = 9.8$ Hz, $J_2 = 3.7$ Hz, H-2), 3.54 (1H, t, $J = 9.4$ Hz, H-4); $^{13}$C NMR $\delta$ 103.6 (1C, d, C-1), 82.9 (1C, d, C-4), 75.1 (1C, d, C-3), 73.9 (1C, d, C-2), 73.4 (1C, d, C-5), 62.2 (1C, t, C-6).

*2,7-dsDPA:* $^1$H NMR $\delta$ 8.22 (2H, s, H-1, H-8), 7.83 (2H, d, $J = 9.4$ Hz, H-4, H-5), 7.76 (2H, d, $J = 9.4$ Hz, H-3, H-6), 7.72 (2H, m, H-3′, H-5′), 7.72 (1H, m, H-4′), 7.68 (2H, m, H-4″), 7.67 (2H, m, H-3″, H-5″), 7.52 (2H, d, $J = 7.3$ Hz, H-2′, H-6′), 7.47 (2H, bd, H-2″, H-6″); $^{13}$C NMR $\delta$ 143.0 (1C, s, C-9), 141.4 (2C, s, C-2, C-7), 139.7 (1C, s, C-1″), 139.4 (1C, s, C-10), 138.8 (1C, s, C-1′), 133.2 (2C, d, C-2′, C-6′), 133.0 (2C, d, C-2″, C-6″), 132.7 (2C, s, C-4a, C-10a), 130.8 (2C, s, C-8a, C-9a), 130.7 (2C, d, C-3′, C-5′), 130.6 (2C, d, C-3″, C-5″), 130.4 (1C, d, C-4′), 130.1 (2C, d, C-4, C-5), 130.1 (1C, d, C-4″), 126.9 (2C, d, C-1, C-8), 124.1 (2C, d, C-3, C-6).

*Host–guest complex of 2,7-dsDPA (**1**) with γ-CD*

*γCD:* $^1$H NMR $\delta$ 5.09 (1H, d, $J = 3.7$ Hz, H-1), 3.89 (1H, t, $J = 9.6$ Hz, H-3), 3.81 (2H, m, H-6, H-6′), 3.78 (1H, m, H-5), 3.64 (1H, bdd, H-2), 3.58 (1H, t, $J = 9.7$ Hz, H-4); $^{13}$C NMR $\delta$ 103.5 (1C, d, C-1), 82.2 (1C, d, C-4), 74.9 (1C, d, C-3), 74.2 (1C, d, C-2), 73.8 (1C, d, C-5), 62.0 (1C, t, C-6).

*2,7-dsDPA:* $^1$H NMR $\delta$ 8.22 (2H, s, H-1, H-8), 7.85 (2H, d, $J = 9.2$ Hz, H-4, H-5), 7.73 (2H, m, H-3′, H-5′), 7.73 (1H, m, H-4′), 7.71 (2H, m, H-3, H-6), 7.66 (2H, m, H-3″, H-5″), 7.66 (1H, m, H-4″), 7.52 (2H, bd, H-2′, H-6′), 7.44 (2H, bd, H-2″, H-6″); $^{13}$C NMR $\delta$ 142.8 (1C, s, C-9), 141.5 (2C, s, C-2, C-7), 139.5 (1C, s, C-10), 139.5 (1C, s, C-1″), 138.7 (1C, s, C-1′), 133.1 (2C, d, C-2′, C-6′), 133.0 (2C, d, C-2″, C-6″), 132.6 (2C, s, C-4a, C-10a), 130.8 (2C, s, C-8a, C-9a), 130.8 (2C, d, C-3″, C-5″), 130.7 (2C, d, C-4, C-5), 130.4 (1C, d, C-4′), 130.3 (2C, d, C-3′, C-5′), 130.1 (1C, d, C-4″), 126.8 (2C, d, C-1, C-8), 123.9 (2C, d, C-3, C-6).

*Host–guest complex of 2,6-dsDPA (**2**) with β-CD*

*βCD:* $^1$H NMR $\delta$ 5.06 (1H, d, $J = 3.7$ Hz, H-1), 3.91 (1H, bt, H-3), 3.86 (2H, m, H-6, H-6′), 3.82 (1H, m, H-5), 3.64 (1H, dd, $J_1 = 9.9$ Hz, $J_2 = 3.7$ Hz, H-2), 3.57 (1H, t, $J = 9.3$ Hz, H-4); $^{13}$C NMR $\delta$ 103.8 (1C, d, C-1), 83.0 (1C, d, C-4), 75.1 (1C, d, C-3), 73.9 (1C, d, C-2), 73.7 (1C, d, C-5), 62.0 (1C, t, C-6).

*2,6-dsDPA:* $^1$H NMR $\delta$ 8.18 (2H, dd, $J_1 = 1.9$ Hz, $J_2 = 0.7$ Hz, H-1, H-5), 7.88 (2H, dd, $J_1 = 9.2$ Hz, $J_2 = 0.7$ Hz, H-4, H-8), 7.71 (2H, dd, $J_1 = 9.2$ Hz, $J_2 = 1.9$ Hz, H-3, H-7), 7.71 (4H, m, H-3′, H-5′), 7.70 (2H, m, H-4′), 7.49 (4H, bdd, H-2′, H-6′); $^{13}$C NMR $\delta$ 141.8 (2C, s, C-2, C-6), 141.0 (2C, s, C-9, C-10), 139.1 (2C, s, C-1′), 133.0 (4C, d, C-2′, C-6′), 132.0 (2C, s, C-4a, C-8a), 131.2 (2C, s, C-9a, C-10a), 130.5 (4C, d, C-3′, C-5′), 130.4 (2C, d, C-4, C-8), 130.3 (2C, d, C-4′), 126.4 (2C, d, C-1, C-5), 123.5 (2C, d, C-3, C-7).

*Host–guest complex of 2,6-dsDPA (**2**) with γ-CD*

*γCD:* $^1$H NMR $\delta$ 5.01 (1H, s, H-1), 3.64 (1H, m, H-3), 3.56 (1H, m, H-2), 3.52 (1H, m, H-4), 3.46 (2H, m, H-6, H-6′), 3.15 (1H, m, H-5); $^{13}$C NMR $\delta$ 103.6 (1C, d, C-1), 81.6 (1C, d, C-4), 74.8 (1C, d, C-3), 74.3 (1C, d, C-2), 73.7 (1C, d, C-5), 61.3 (1C, t, C-6).

*2,6-dsDPA:* $^1$H NMR $\delta$ 8.16 (2H, s, H-1, H-5), 7.81 (2H, m, H-4, H-8), 7.66 (2H, m, H-3, H-7), 7.64 (4H, m, H-3′, H-5′), 7.64 (2H, m, H-4′), 7.47 (4H, m, H-2′, H-6′); $^{13}$C NMR $\delta$((132.8 (4C, d, C-2′, C-6′), 130.8 (2C, d, C-4, C-8), 126.8 (2C, d, C-1, C-5), 123.5 (2C, d, C-3, C-7).

More detailed assignment of carbon signals was not possible, because $^{13}$C NMR spectra contained broad bands (assigned signals were identified from gHSQC).

*Host–guest complex of 2,7-dsDPA$O_2$ (**3**) with β-CD*

*βCD:* $^1$H NMR $\delta$ 5.03 (1H, d, $J = 3.8$ Hz, H-1), 3.88 (1H, t, $J = 9.5$ Hz, H-3), 3.85 (2H, m, H-6, H-6′), 3.71 (1H, m, H-5), 3.59 (1H, dd, $J_1 = 9.9$ Hz, $J_2 = 3.7$ Hz, H-2), 3.55 (1H, t, $J = 9.5$ Hz, H-4); $^{13}$C NMR $\delta$ 103.7 (1C, d, C-1), 82.9 (1C, d, C-4), 75.1 (1C, d, C-3), 73.9 (1C, d, C-2), 73.8 (1C, d, C-5), 62.0 (1C, t, C-6).

*2,7-dsDPA$O_2$:* $^1$H NMR $\delta$ 7.95 and 7.82 (2H, dd, $J_1 = 8.1$ Hz, $J_2 = 1.7$ Hz, H-3, H-6), 7.80 (2H, m, H-2′, H-6′), 7.81 (2H, m, H-3″, H-5″), 7.74 (2H, m, H-2″, H-6″), 7.72–7.82 (2H, m, H-3′, H-5′), 7.72–7.78 (1H, m, H-4′), 7.72–7.78 (1H, m, H-4″), 7.69 and 7.67 (2H, d, $J = 1.8$ Hz, H-1, H-8), 7.38 and 7.32 (2H, d, $J = 8.1$ Hz, H-4, H-5); $^{13}$C NMR $\delta$ 144.66 and 144.65 (2C, s, C-2, C-7), 144.00 and 143.71 (2C, s, C-4a, C-10a), 142.05 and 141.83 (2C, s, C-8a, C-9a), 133.5 (1C, s, C-1′), 132.7 (1C, s, C-1″), 131.2 (1C, d,

C-4″), 131.1 (2C, d, C-2′, C-6′), 131.0 (1C, d, C-4′), 130.6 (2C, d, C-2″, C-6″), 129.0 (2C, d, C-3′, C-5′), 129.0 (2C, d, C-3″, C-5″), 127.76 and 127.69 (2C, d, C-3, C-6), 125.96 and 125.84 (2C, d, C-4, C-5), 122.9 (2C, d, C-1, C-8), 86.2 (1C, s, C-9), 85.9 (1C, s, C-10).

*Host–guest complex of 2,7-dsDPAO$_2$ (**3**) with γ-CD*

*γCD:* $^1$H NMR δ 5.11 (1H, d, $J$ = 4.0 Hz, H-1), 3.93 (1H, t, $J$ = 9.5 Hz, H-3), 3.83 (2H, m, H-6, H-6′), 3.81 (1H, m, H-5), 3.65 (1H, dd, $J_1$ = 9.9 Hz, $J_2$ = 3.9 Hz, H-2), 3.60 (1H, t, $J$ = 9.3 Hz, H-4); $^{13}$C NMR δ 103.6 (1C, d, C-1), 82.3 (1C, d, C-4), 74.9 (1C, d, C-3), 74.3 (1C, d, C-2), 73.8 (1C, d, C-5), 62.1 (1C, t, C-6).

*2,7-dsDPAO$_2$:* $^1$H NMR δ 7.79 (2H, m, H-3″, H-5″), 7.785 and 7.775 (2H, m, H-3, H-6), 7.77 (2H, m, H-2′, H-6′), 7.72 (2H, m, H-2″, H-6″), 7.68–7.79 (2H, m, H-3′, H-5′), 7.68–7.79 (1H, m, H-4′), 7.68–7.79 (1H, m, H-4″), 7.665 and 7.655 (2H, d, $J$ = 1.6 Hz, H-1, H-8), 7.405 and 7.395 (2H, d, $J$ = 8.1 Hz, H-4, H-5); $^{13}$C NMR δ 144.86 and 144.81 (2C, s, C-2, C-7), 143.71 and 143.69 (2C, s, C-4a, C-10a), 141.90 and 141.87 (2C, s, C-8a, C-9a), 133.2 (1C, s, C-1′), 132.7 (1C, s, C-1″), 131.3 (1C, d, C-4′), 131.3 (1C, d, C-4″), 131.2 (2C, d, C-2′, C-6′), 130.9 (2C, d, C-2″, C-6″), 129.1 (2C, d, C-3′, C-5′), 129.0 (2C, d, C-3″, C-5″), 127.69 and 127.67 (2C, d, C-3, C-6), 126.54 and 126.49 (2C, d, C-4, C-5), 122.9 (2C, d, C-1, C-8), 86.5 (1C, s, C-9), 86.3 (1C, s, C-10).

*Host–guest complex of 2,6-dsDPAO$_2$ (**4**) with β-CD*

*βCD:* $^1$H NMR δ 5.05 (1H, d, $J$ = 3.8 Hz, H-1), 3.91 (1H, t, $J$ = 9.5 Hz, H-3), 3.86 (2H, m, H-6, H-6′), 3.77 (1H, m, H-5), 3.62 (1H, dd, $J_1$ = 10.0 Hz, $J_2$ = 3.6 Hz, H-2), 3.57 (1H, t, $J$ = 9.4 Hz, H-4); $^{13}$C NMR δ 103.8 (1C, d, C-1), 83.0 (1C, d, C-4), 75.0 (1C, d, C-3), 74.0 (1C, d, C-2), 73.8 (1C, d, C-5), 62.1 (1C, t, C-6).

*2,6-dsDPAO$_2$:* $^1$H NMR δ 7.79 and 7.77 (2H, dd, $J_1$ = 8.0 Hz, $J_2$ = 1.7 Hz, H-3, H-7), 7.76 (4H, m, H-2′, H-6′), 7.76 (4H, m, H-3′, H-5′), 7.70 (2H, m, H-4′), 7.660 and 7.655 (2H, d, $J$ = 2.3 Hz, H-1, H-5), 7.40 and 7.41 (2H, d, $J$ = 8.2 Hz, H-4, H-8); $^{13}$C NMR δ 144.7 (2C, s, C-2, C-6), 143.9 (2C, s, C-4a, C-8a), 141.5 (2C, s, C-9a, C-10a), 132.9 (2C, s, C-1′), 131.1 (2C, d, C-4′), 130.9 (4C, d, C-2′, C-6′), 128.9 (4C, d, C-3′, C-5′), 127.7 (2C, d, C-3, C-7), 126.5 (2C, d, C-4, C-8), 122.8 (2C, d, C-1, C-5), 86.3 (2C, s, C-9, C-10).

*Host–guest complex of 2,6-dsDPAO$_2$ (**4**) with γ-CD*

*γCD:* $^1$H NMR δ 5.02 (1H, d, $J$ = 3.6 Hz, H-1), 3.72 (1H, t, $J$ = 10.0 Hz, H-3), 3.62 and 3.52 (2H, m, H-6, H-6′), 3.58 (1H, m, H-2), 3.55 (1H, m, H-4), 3.40 (1H, m, H-5). $^{13}$C NMR δ 103.7 (1C, d, C-1), 81.9 (1C, d, C-4), 74.8 (1C, d, C-3), 74.3 (1C, d, C-2), 73.7 (1C, d, C-5), 61.3 (1C, t, C-6).

*2,6-dsDPAO$_2$:* $^1$H NMR δ 7.78 (2H, m, H-3, H-7), 7.76 (4H, m, H-3′, H-5′), 7.75 (4H, m, H-2′, H-6′), 7.70 (2H, m, H-4′), 7.65 (2H, s, H-1, H-5), 7.42 (2H, bd, H-4, H-8); $^{13}$C NMR δ 144.8 (2C, s, C-2, C-6), 143.8 (2C, s, C-4a, C-8a), 141.7 (2C, s, C-9a, C-10a), 132.9 (2C, s, C-1′), 131.3 (2C, d, C-4′), 131.0 (4C, d, C-2′, C-6′), 129.0 (4C, d, C-3′, C-5′), 127.7 (2C, d, C-3, C-7), 126.6 (2C, d, C-4, C-8), 122.9 (2C, d, C-1, C-5), 86.6 (2C, s, C-9, C-10).

## Results and discussion

The ability of inclusion complex formation is common property of cyclodextrins. We studied the formation of host–guest complexes of native CDs (β-CD and γ-CD) with singlet oxygen acceptors **1**, **2** and their endoperoxides **3**, **4**. Compounds **1** and **2** were prepared by sulfonation of 9,10-diphenylanthracene with oleum [18, 19]. Endoperoxides **3** and **4** were prepared by reaction of **1**, **2** with $^1O_2$ by using $H_2O_2/MoO_4^{2-}$ system (Scheme 1) [20–23].

$^1$H NMR spectroscopy was used to obtain further information on CDs complexation. The induced shift, Δδ, is defined as the difference in chemical shifts in presence and absence of the guest molecules: $\Delta\delta = \delta_{(\text{complex})} - \delta_{(\text{free})}$. In this convention, positive and negative values show a downfield and upfield shifts, respectively [11, 12].

Chemical shift variations of specific host or guest nucleus can provide evidence of the inclusion complexes formation in solution, since significant changes in micro-environment occur between the free and bound states (especially, when the guest is an aromatic molecule with high anisotropy). Information about the interaction of the four guests with two CDs (β-CD and γ-CD) from NMR was primarily inferred from the changes in chemical shifts. The $^1$H induced shifts of CDs in the presence of the four aromatic molecules are shown in Tables 2 and 3.

The upfield shifts of the protons located within or near the CD cavity (i.e., H-3, H-5, H-6,6′) can be regarded as evidence of the existence of an interaction between the guest molecule and the interior of the host cavity, with a partial or complete inclusion, hence, complexation. It was found that compounds **1**, **2** and their corresponding end-operoxides **3** and **4** form the host–guest complexes with CDs (β-CD and/or γ-CD).

Two-dimensional ROESY experiments have been frequently applied successfully in the elucidation of structures of chemically modified CDs [11, 24] and more recently to prove through-space intermolecular interactions in CDs complex [11, 25]. While the $^1$H chemical shifts provides unambiguous evidence of the complex formation, NOESY

**Table 2** Chemical shift changes ($\Delta\delta$ ppm: negative values correspond to diamagnetic shifts) of $^1$H NMR signals of $\beta$-CD in mixtures with **1–4** compared to the solutions without guest substrate

| | Internal $\beta$-CD protons | | | External $\beta$-CD protons | | |
|---|---|---|---|---|---|---|
| | H-3 | H-5 | H-1 | H-2 | H-4 | H-6, 6′[a] |
| **1** | −0.12 | −0.06 | −0.02 | −0.03 | −0.02 | 0.01 |
| **2** | −0.03 | −0.02 | 0.01 | 0.01 | 0.01 | 0 |
| **3** | −0.06 | −0.13 | −0.02 | −0.04 | −0.01 | −0.01 |
| **4** | −0.03 | −0.07 | 0 | −0.01 | 0.01 | 0 |

Molar ratio of 1–4:$\beta$-CD was 2:1

[a] H-6,6′ of $\beta$-CD are unresolved

**Table 3** Chemical shift changes ($\Delta\delta$ ppm: negative values correspond to diamagnetic shifts) of $^1$H NMR signals of $\gamma$-CD in mixtures with **1–4** compared to the solutions without guest substrate

| | Internal $\gamma$-CD protons | | | External $\gamma$-CD protons | | |
|---|---|---|---|---|---|---|
| | H-3 | H-5 | H-1 | H-2 | H-4 | H-6, 6′[a] |
| **1** | −0.05 | −0.10 | −0.03 | −0.02 | −0.02 | −0.07 |
| **2** | −0.28 | −0.68 | −0.11 | −0.10 | −0.08 | −0.37 |
| **3** | −0.01 | −0.07 | −0.01 | −0.01 | 0 | −0.05 |
| **4** | −0.22 | −0.48 | −0.10 | −0.08 | −0.05 | [a] |

Molar ratio of **1–4**:$\gamma$-CD was 2:1

[a] H-6,6′ of $\gamma$-CD are unresolved, only in the mixture **4**:$\gamma$-CD are identified −0.36 and −0.28

**Table 4** 2D-ROESY (2D-NOESY) cross-peaks [strong (++), medium (+) or absence (−)] between guest molecules **1–4** and $\beta$-CD in $D_2O$ solution

| | Internal $\beta$-CD protons | | | External $\beta$-CD protons | | |
|---|---|---|---|---|---|---|
| | H-3 | H-5 | H-1 | H-2 | H-4 | H-6, 6′[a] |
| **1** | | | | | | |
| H-2″ | ++ | + | − | − | − | + |
| H-3″ | + | ++ | − | − | + | ++ |
| H-3 | + | − | − | − | − | + |
| H-4 | ++ | − | − | + | − | + |
| **2** | | | | | | |
| H-2′ | − | − | − | − | − | − |
| H-3′ | − | − | − | − | − | − |
| H-3 | − | − | − | − | − | − |
| H-4 | − | − | − | − | − | − |
| **3** | | | | | | |
| H-2″ | ++ | ++ | − | + | + | − |
| H-3″ | ++ | ++ | − | + | + | − |
| H-1 | − | − | − | − | − | − |
| H-3 | + | − | − | + | − | − |
| H-4 | + | + | − | + | + | − |
| **4** | | | | | | |
| H-2′, 3′ | − | + | − | − | + | + |
| H-4′ | − | − | − | − | − | + |
| H-4 | − | − | − | − | − | − |
| H-1 | − | − | − | − | − | + |

Molar ratio of **1–4**:$\beta$-CD was 2:1

[a] H-6,6′ of $\beta$-CD are unresolved

or ROESY experiments have been demonstrated to provide information on the dynamics and the averaged relative inter- and intramolecular proton distances [8, 25]. In the present study ROESY spectra were acquired to gain further information on the inclusion complexation mode and additional insights into the dynamic structure. Due to the rapid dynamics of the complexation process, the NOE effects were used only qualitatively and no conclusions on intermolecular distances were extracted. Only relative amounts of host–guest complexes in solution were estimated from the relative intensities of cross-peaks. The through-space contacts with relative intensity of corresponding cross-peaks for all complexes are summarized in the Tables 4 and 5.

## Host–guest complexes of 2,7-ds-DPA with CDs

Considering the $^1$H NMR spectra of mixtures of **1** with $\beta$-CD and $\gamma$-CD it is obvious that formation of inclusion complex occurred with both CDs.

For the complex **1**:$\beta$-CD we have observed the largest differences in $^1$H NMR chemical shifts of cyclodextrin protons H-3 and H-5, located inside the cavity (see Table 2). The large amount of relatively intensive cross-peaks found in ROESY spectra indicate that complex of **1** with $\beta$-CD was formed via deep insertion of phenyl group more distant from sulfonated part of **1** into the cavity of $\beta$-CD by its "secondary face" (broad end) (see Table 4, Figs. 1, 2). Some lower intensity cross-peaks, for example contacts between H-6,6′ of $\beta$-CD and H-3, H-4 and H-2″ of **1**, can also indicate a small amount of host–guest complex with other binding mode, e.g. via "primary face" (narrow end) complex. These contacts can not be explained trough inclusion of phenyl group into the cavity $\beta$-CD via "secondary face". However, the amount of this type is lower than the amount of complex with binding mode through the "secondary face" of $\beta$-CD.

In the case of **1**:$\gamma$-CD we observed chemical shift changes of proton signals of $\gamma$-CD, especially H-5 and H-6,6′ and less of H-3, due to complexation (see Table 3). The ROESY cross-peaks (see Table 5) indicate formation of the complex with shallow inclusion of phenyl group located far from the sulfonated part of **1** into the cavity $\gamma$-CD via "primary face" (narrow end), (Scheme 1, Fig. 1). All observed cross-peaks have low intensity, and this fact points to relatively small amount of formed complex.

Host–guest complexes of 2,6-ds-DPA with CDs

NMR spectra of 2,6-dsDPA:CDs show that compound **2** forms inclusion complex only with $\gamma$-CD.

**Table 5** 2D-ROESY (2D-NOESY) cross-peaks [strong (++), medium (+) or absence (−)] between guest molecules **1**–**4** and $\gamma$-CD in $D_2O$ solution

| | Internal $\gamma$-CD protons | | | External $\gamma$-CD protons | | |
|---|---|---|---|---|---|---|
| | H-3 | H-5 | H-1 | H-2 | H-4 | H-6, 6′[a] |
| **1** | | | | | | |
| H-2″ | − | +[b] | − | − | − | +[b] |
| H-3″ | − | +[b] | − | − | − | +[b] |
| H-3 | − | +[b] | − | − | − | +[b] |
| H-4 | − | +[b] | − | − | − | +[b] |
| **2** | | | | | | |
| H-2′ | + | + | − | − | + | + |
| H-3′ | − | + | − | − | − | − |
| H-3 | + | − | − | − | + | − |
| H-4 | + | ++ | − | − | + | + |
| **3** | | | | | | |
| H-2″ | + | ++ | − | − | + | ++ |
| H-3″ | + | ++ | − | − | − | ++ |
| H-1 | − | + | − | − | − | + |
| H-3 | + | + | − | − | − | + |
| H-4 | − | − | − | − | − | − |
| **4** | | | | | | |
| H-2′, 3′ | + | + | − | − | − | ++ |
| H-4′ | − | − | − | − | − | − |
| H-4 | − | + | − | − | − | + |
| H-1 | − | − | − | − | − | − |

Molar ratio of 1–4:$\gamma$-CD was 2:1

[a] H-6,6′ of $\gamma$-CD are unresolved

[b] Cross-peaks can not be exactly assigned contacts of **1** with H-5 and/or H-6,6′ of $\gamma$-CD

No cross-peaks were found in the ROESY spectra of **2**:$\beta$-CD (Table 4). It can be explained by the absence or very small amount of the host–guest complex.

In $^1$H NMR spectra of **2**:$\gamma$-CD we observed large differences in chemical shift of H-5 and H-6,6′ proton signals and less of H-3 of $\gamma$-CD (see Table 3). From the positions of the cross-peaks in the ROESY spectra it is possible to claim that inclusion of phenyl group of **2** into the cavity of $\gamma$-CD via "primary face" has occurred (Table 5). However, this interaction is not analogous to the interaction of **1**:$\gamma$-CD. In this case, non-sulfonated part of compound **2** is inserted relatively deeply and in somewhat tilted manner into the cavity of $\gamma$-CD (see Fig. 2). It is confirmed also by absence of cross-peaks corresponding to the interaction of H-1 of **2** with H-5 eventually H-6,6′ of $\gamma$-CD. On the other hand this interaction was observed with H-4 of **2** (see Table 5). This mode of interaction can be explained by sterical hindrance of sulfonated groups of **2**. In the case of **1** both sulfonate groups are far from interacting phenyl and therefore this type of complex was not observed.

Host–guest complexes of 2,7-ds-DPA$O_2$ with CDs

Measurement of NMR spectra of 2,7-dsDPA$O_2$ with CDs proved that synthesized endoperoxide **3** forms also complexes with both native CDs, as well as in the case of **1**.

$^1$H-NMR and $^{13}$C-NMR spectra of **3** with both CDs proved existence of chiral cyclodextrin molecule in the proximity of phenyl group of **3** located far from sulfonate groups. It arises from the presence of double proton and carbon signals corresponding to enantiotopic (diastereotopic in the presence of CDs) atoms of the anthracene ring system (see experimental section). This effect does not occur in complexes of **1** with CDs, due to absence of the peroxy group in **1**. Molecule **1** is planar and corresponding protons and carbons are equivalent even in the presence of chiral cyclodextrin molecules. Differences in chemical shifts of protons in $^1$H-NMR increase with increasing

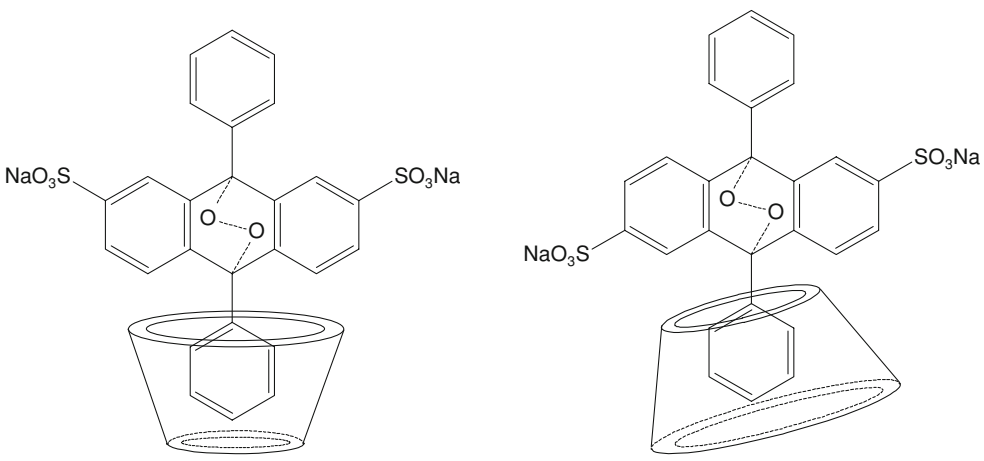



**Fig. 2** The model structure host–guest complexes of **1** and **3** with $\beta$-CD (**1**:$\beta$-CD, **3**:$\beta$-CD) and **2** and **4** with $\gamma$-CD (**2**:$\gamma$-CD, **4**:$\gamma$-CD)

proximity of anthracene core of **3** to the chiral cyclodextrin molecule.

Formation of inclusion complex **3**:$\beta$-CD was proved also by ROESY spectra (see Table 4). From the large number of intensive cross-peaks it can be concluded that the complex was formed via deep insertion of phenyl group more distant from sulfonated part of **3** into the cavity of $\beta$-CD through its "secondary face" (see Fig. 2). Furthermore, intensities of the cross-peaks indicate formation of relatively stable complex. Signals corresponding to H-3 and H-6,6′ of $\beta$-CD overlap in $^1$H NMR, and therefore weak contacts of H-6,6′of $\beta$-CD with proton signals of **3,** are unclean. These contacts together with space contacts of H-2 of $\beta$-CD with H-3 and H-4 of **3** would indicate formation of complex via insertion of phenyl group more distant from sulfonated part of **3** into the cavity of $\beta$-CD by its "primary face" with lower stability. Similar contacts were found also in ROESY spectra of **1**:$\beta$-CD.

Measurement of ROESY spectra also proved that endoperoxide **3** forms inclusion complex with $\gamma$-CD. Illustration of 2D-NMR (ROESY) spectrum of the host–guest complex is on the Fig. 3. Space contacts suggest formation of inclusion complex with shallow insertion of phenyl group more distant from sulfonated part of **3** into the cavity of $\gamma$-CD, like in the case of complex **1**:$\gamma$-CD (Table 5). Relatively high stability of the complex **3**:$\gamma$-CD can be estimated from intensity of the cross-peaks.

Weak contacts corresponding to the interaction between H-5, H-6,6′ of $\gamma$-CD with H-1 of **3** were also found in ROESY spectra (see Table 5). These interactions can be explained by presence of low amount of inclusion complex formed via insertion of phenyl group close to sulfonated part of **3** into the cavity of $\beta$-CD by its "primary face".

## Host–guest complexes of 2,6-ds-DPAO$_2$ with CDs

Measurement of NMR spectra has shown that endoperoxide **4** forms inclusion complexes with both $\beta$-CD and $\gamma$-CD. In contrast to endoperoxide **3**, compound **4** is chiral molecule. Molecule **4** has two enantiomeric structures in molar ratio 1:1 with respect to the method of preparation, each of them generate independent diastereomeric complexes.

However, chemical shift changes in $^1$H NMR spectra for **4**:$\beta$-CD are imponderable and no spitting of the spectra into two sets of signals as in the case of **3**:$\beta$-CD was observed. In conjunction with low intensity of cross-peaks found in ROESY spectra, very low stability of forming complex is suggested. ROESY contacts and their relative intensity indicate formation of complex via minimal insertion of phenyl group of **4** to the cavity of $\beta$-CD by its "primary face". However, formation of non-specific external binding between the $\beta$-CD exterior and **4** in the complex is not expected.

Complex **4**:$\gamma$-CD contains a number of narrow and broad signals in $^1$H NMR spectra, which in conjunction with exchange cross-peaks in ROESY indicate slow interconversion between various structures. However, one main set of signals could be identified in the spectra. Both chemical shift changes and ROESY cross-peak indicate formation of complex **4**:$\gamma$-CD via insertion of phenyl group of **4** into the cavity of $\gamma$-CD like in the case of **2**:$\gamma$-CD (Table 3 and 5, Fig. 2). Relatively weak cross-peaks

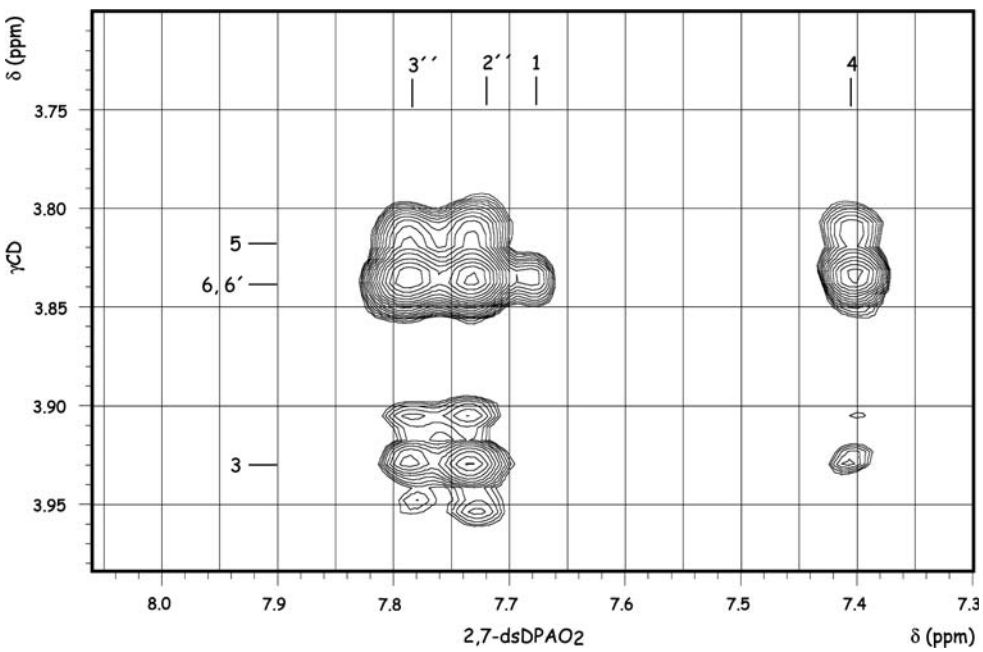



**Fig. 3** 2D-NMR (ROESY) spectrum of the host–guest complex 2,7-dsDPAO$_2$ with $\gamma$-CD (**3**:$\gamma$-CD)

corresponding to space contacts of cyclodextrin H-5 with H-2′ and H-3 of **4** can be explained by the presence of more structures and different population of diastereomeric complexes.

## Conclusion

We have found that water-soluble anthracene carriers of singlet oxygen **1**, **2** and corresponding endoperoxides **3**, **4** form host–guest complexes with native $\beta$- and $\gamma$-CD. Detailed insights of geometries were obtained and two binding modes of interaction were recognized on the basis of NMR spectroscopy. Chemical shift changes in $^1$H NMR spectra and space contact in 2D NMR experiments have shown binding modes: (i) inclusion of guest molecules via the "secondary face" (narrow end) into the cavity of CDs. This is a typical mode for complexes of **1** and **3** with $\beta$-CD; (ii) inclusion of guest molecules via the "primary face" into the cyclodextrin cavity. This mode of interaction was found for host–guest complexes of **2** and **4** with $\gamma$-CD. Small amount of inclusion complex indicating formation of host–guest interaction via "primary face" was found also in the case of **1** and **3** with $\beta$-CD. The size of cavity of $\beta$-CD is in comparison to size of $\gamma$-CD smaller thereby inclusion via "secondary face" (broad end) was more likely founded for complexes of $\beta$-CD. The formation of inclusion complex of **2** with $\beta$-CD was not observed. This is in agreement with previously obtained spectrophotometric data [18]. Compounds **1** and **3** form symmetric inclusion complexes with $\gamma$-CD in contrast to tilted host–guest complexes of **2** and **4** with $\gamma$-CD. This observation can be rationalized by steric hindrance of the sulfonate groups. Modes of interaction and stabilities of complexes are similar for an endoperoxides and its parent anthracene derivatives. Host–guest complexes of cyclodextrins with both $^1O_2$ acceptors **1** and **2** and endoperoxides (secondary sources of $^1O_2$) **3** and **4** can be used in biological applications and for several mechanistic $^1O_2$ studies or organic synthesis.

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