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ScienceDirect
Tetrahedron
Tetrahedron 62 (2006) 9701–9704

Synthesis and inclusion capability of a β-cyclodextrin-tetrathiafulvalene derivative

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Received 25 April 2006; revised 7 July 2006; accepted 25 July 2006
Available online 17 August 2006

Abstract—The synthesis of 4,5-ethylenedithio-4′-[6-deoxy-β-cyclodextrin-6-yl-aminocarbonyl]-tetrathiafulvalene **3** is reported. Dominantly, the structure of **3** has been established on the basis of mass spectrometry, ROESY and ^{1}H NMR spectra, combined with a theoretical MM3 study, indicating an 'open-cavity structure'. The sensing ability of **3** and the formation constant of the complex [(**3**)-(1-adamantanol)] have been evaluated experimentally by UV–vis spectroscopy and theoretically by the MM3 docking procedure method.

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1. Introduction

During the past decade much effort has been devoted to developing analysis systems for the detection of chemical and biological compounds, without any modification of the analytes.[1–5] Some chemically modified cyclodextrins (CDs) form relatively stable host-guest complexes, due to their inclusion capability, with a large variety of organic compounds.[6,7] Such derivatives might be useful for constructing molecule-sensing systems.[8–13] In previous papers we reported the synthesis[14–17] and sensing abilities[18,19] towards volatile organic compounds (VOC) of a new class of fluorescent sensors based on β-cyclodextrin fragment (β-CD) and indolizine unit. On the other hand, electrochemical sensors based on tetrathiafulvalene (TTF), a redox active unit extensively studied in the field of conducting molecular materials,[20] and various receptors such as crown ethers,[21] calix-arenes[22] or calix-pyrroles[23] have proved their efficiency in the sensing of anions or metallic cations. Therefore, the covalent association of the cyclodextrin platform with a TTF derivative appears to be particularly attractive in the prospective of controlling the host TTF–cyclodextrin—guest interaction through an electrochemical switch. At our knowledge, only two reports in the literature deal with covalent TTF–cyclodextrin derivatives,[24] prepared as precursors for Langmuir–Blodgett films, whereas inclusion TTF–cyclodextrin complexes have been used as mediators in the glucose–glucose oxidation reaction.[25] We report herein the synthesis and characterization of a new type of sensor consisting of β-CD and TTF units covalently linked, together with its sensing ability towards the 1-adamantanol.

2. Results and discussion

2.1. Synthesis

The covalent link between the β-CD and TTF units has been performed upon reaction of 6-deoxy-6-aminocyclodextrin **1**[26] and 4,5-ethylenedithio-4′-chlorocarbonyl-tetrathiafulvalene (EDT–TTF–COCl) **2** in homogenous phase in dry DMF, under argon, thus providing the mixed β-CD–TTF derivative **3** (Scheme 1). Indeed, the reaction of **2** with various primary amines has been described as a straightforward method for the preparation of EDT–TTF–amides.[27] The chemical structure of **3** has been established by NMR and mass spectra. In the latter, the presence of [M$^+$+23] at 1477 and [β-CD+CO+23]$^+$ at 1185 fragments prove undoubtedly the proposed molecular structure. In order to assign all the chemical shifts of the protons, the ^{1}H NMR spectra have been performed in two different solvents, e.g., DMSO-d_6 and D_2O. The ROESY 2D spectrum, measured in D_2O, shows clearly the lack of interaction between the TTF fragment and the CD cavity, very likely because of

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Keywords: β-Cyclodextrine; Tetrathiafulvalene; Inclusion; 1-Adamantanol; Open cavity.

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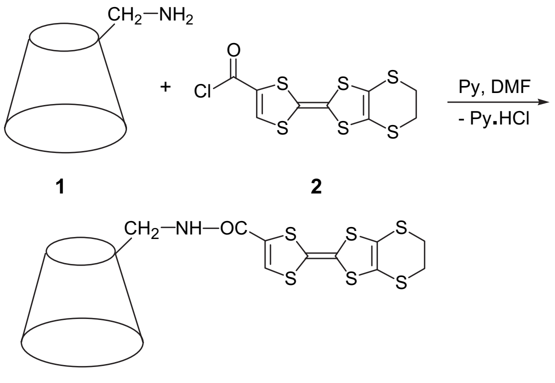
doi:10.1016/j.tet.2006.07.088

the short covalent link between the TTF and the CD, thus preventing the inclusion of the former in the latter.



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Scheme 1. Synthesis of 4,5-ethylenedithio-4′-[6-deoxy-β-cyclodextrin-6-yl-aminocarbonyl]-tetrathiafulvalene **3**.

2.2. Inclusion of 1-adamantanol

The evaluation of the host inclusion ability towards 1-adamantanol has been carried out by UV–vis spectroscopy combined with the well-known direct titration method. For a 1:1 molar ratio, the calculation of the formation constant K_f was developed as follows:

$$\text{HOST} + \text{GUEST} \rightleftarrows \text{HOST/GUEST}$$

$$K_f = \frac{[\text{HOST/GUEST}]}{[\text{HOST}]^{*}[\text{GUEST}]} \tag{1}$$

$$K_f = \frac{[\text{HOST/GUEST}]}{([\text{GUEST}]_T - [\text{HOST/GUEST}]) - ([\text{HOST}]_T - [\text{HOST/GUEST}])} \tag{2}$$

$$[\text{HOST/GUEST}] = -\frac{1}{2}\sqrt{\left[\left(\frac{1}{K_f} + [\text{HOST}]_T + [\text{GUEST}]_T\right)^2 - 4[\text{HOST}]_T[\text{GUEST}]_T\right]} + \frac{1}{2}\left(\frac{1}{K_f} + [\text{HOST}]_T + [\text{GUEST}]_T\right) \tag{3}$$

where K_f and T stand for formation constant and total, respectively. For a given value of K_f the [HOST/GUEST] concentration is known, thus allowing the calculation of the molecular absorptivity of the inclusion compound. An algorithm treatment was then applied to minimize the difference of the spectral characteristics over the various solutions.

The absorbance of the host was recorded in function of different concentrations of the added guest. The spectral variations, although weak, lead to well defined isobestic points. The data fit well with a 1:1 binding isotherm, especially for the 265–280 nm range concerned by the strongest spectral modifications. The resulting value of the formation constant, amounting at 1538 M^{-1}, shows that the newly synthesized β-CD–TTF derivative still possesses inclusion properties, which could eventually vary upon changing the TTF oxidation state (Figs. 1 and 2).

2.3. Molecular modelling

The docking of the guest (1-adamantanol) with respect to the locked β-CD unit has been performed using three dummy atoms, in such a way that the molecule of 1-adamantanol crosses the cyclodextrin ring while making a continuous rotation (Fig. 3).

Two regiochemical ways E1 and E2 have been considered. By A and B are notified the two atoms from 1-adamantanol taken into account in defining distances A-D2 and B-D2, also the dihedral angles A-D1-D2-D3-D4 and B-D1-D2-D3.

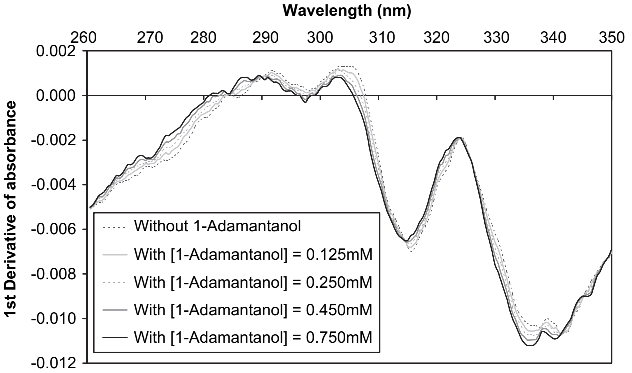

Figure 1. First derivative of the UV spectra of the TTF modified β-cyclodextrin in the absence and presence of increasing concentrations of 1-adamantanol.

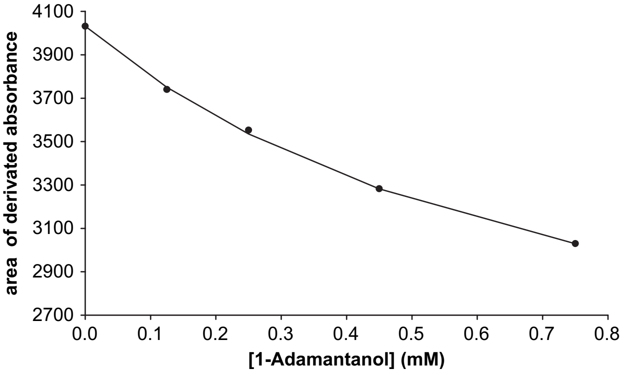

Figure 2. Adjustment, in function of the guest concentration, between the experimental area of the first derivative of absorbance (discrete points) and the theoretical values (continuous line) according to a 1:1 equilibrium.

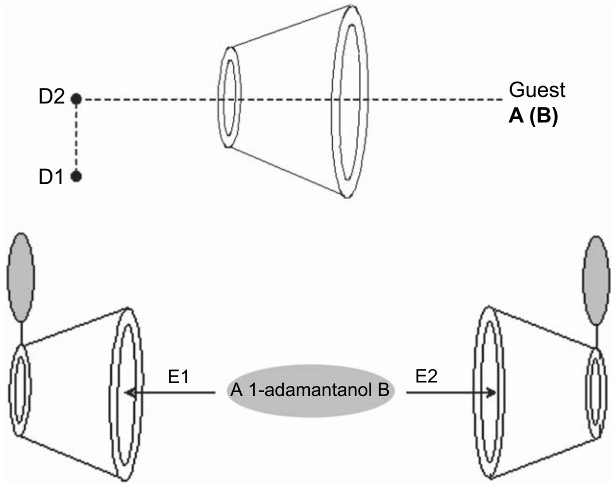

Figure 3. Docking and regiochemical ways.

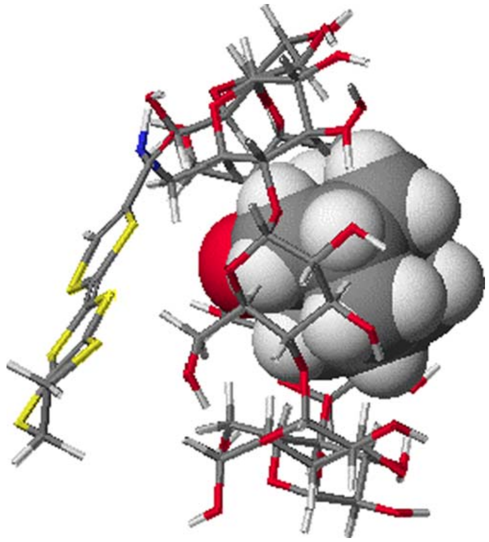

Figure 4. Complex CD–TTF(**3**)-1-adamantanol.

The most stable configuration of the inclusion complex CD–TTF **3** with the 1-adamantanol, obtained by the MM3 method, is shown in Figure 4.

The computed complexation energy ΔE, corresponding to the difference between the potential energy of the inclusion complex and the sum of their individual components in their optimized ground states, amounts at −10.92 Kcal/mol. Such a value is in good agreement with those for other host-guest complexes.[19,28]

3. Conclusions

A water soluble β-cyclodextrin–TTF derivative has been synthesized and characterized. Its inclusion properties towards the guest 1-adamantanol have been experimentally and theoretically determined. The compound described herein represents the first step in the elaboration of a new class of water soluble electroactive sensing systems. The inclusion of other molecules, as well as the TTF electrochemical response, is currently under investigation in our groups.

4. Experimental

4.1. General comments

^{1}H NMR spectra were recorded with a Bruker AM 400 spectrometer with tetramethylsilane (TMS) as an internal standard. Chemical shift values δ are reported in parts per million and coupling constants J are in hertz. The following abbreviations have been used: s (singlet), d (doublet), m (multiplet), C (cyclodextrin). Mass spectra were measured using a Platform II Micromass Apparatus. IR spectra were recorded on a Perkin–Elmer instrument. Melting point was obtained with a Reichert Thermopan apparatus and is uncorrected. Chromatographic separation was carried out on Sephadex G15.

4.2. Synthesis of 4,5-ethylenedithio-4′-[6-deoxy-β-cyclodextrin-6-yl-aminocarbonyl]-tetrathiafulvalene 3

In a 100-mL round-bottomed flask 0.567 g (0.5 mmol) 6-deoxy-6-aminocyclodextrin (**1**) was dissolved in dry DMF (35 mL). Then, 0.178 g (0.5 mmol) solid 4,5-ethylenedithio-4′-chlorocarbonyl-tetrathiafulvalene was gradually added under stirring. To the stirred reaction mixture pyridine (0.08 mL) in DMF (5 mL) was added over a period of 15 min using a dropping funnel. Stirring under argon and warming (65 °C) of the reaction mixture were continued for 14 h. After cooling the mixture was poured drop wise into acetone (100 mL). The resulting precipitate was collected and washed with acetone. The crude solid was dissolved in distilled water (50 mL), filtered and then concentrated to provide 10 mL of solution, which was purified on a Sephadex G-15 column to give the compound **3** as a yellow-orange powder. Yield 47%. Mp=220 °C, dec. IR (KBr, cm^{-1}): 3390, 1634 ($\nu_{C=O}$), 1385, 1156, 1029. ^{1}H NMR (DMSO-d_6): δ 7.99 (m, 1H, NH), 6.69 (s, 1H, =CH), 5.92–5.75 (m, 14H, –OH-2$_C$, –OH-3$_C$), 4.98–4.80 (m, 7H, H-1$_C$), 4.60–4.42 (m, 8H, –O–CH$_{2C}$–, –OH-6$_C$), 3.85–3.10 (m, 44H, H-2$_C$, H-4$_C$, H-3$_C$, H-5$_C$, H-6$_C^{A,B}$, S–CH_2–CH_2–S). ^{1}H NMR (D$_2$O): δ 8.01–7.85 (m, 1H, NH), 7.03 (s, 1H, =CH), 5.05–4.90 (m, 7H, CH-1$_C$), 4.74–4.63 (H$_2$O+–OH 2$_C$,3$_C$,6$_C$), 3.97–3.73 (m, 28H, CH–3$_C$,5$_C$,6$_C$^{AB}), 3.57–3.51 (m, 14H, CH-2$_C$,4$_C$), 3.53–3.44 (m, 4H, S–CH_2–CH_2–S). MS (ES$^+$, cone 40) *m*/*z* (%): 1447 (M+23) (15%), 1157 (CD-6-yl-NH+23) (80%), 1185 (CD-6-yl-NH–CO+23) (100%). Anal. calcd for $C_{51}H_{75}NO_{35}S_6$: C, 42.11; H, 5.20; S, 13.23. Found: C, 40.56; H, 4.85; S, 12.64.

4.3. UV–vis spectroscopy

Spectra were recorded at 298 K using a Perkin–Elmer Lambda 2S double beam spectrometer and a quartz cell with optical path length of 1 cm. The compounds were dissolved in phosphate buffer at pH 5.8. All spectra were used in the derivative form in order to avoid the influence of diffraction on the titration experiment.

4.4. Molecular modelling

Compound **3** and 1-adamantanol were built starting from data provided by the Cambridge Structural Data Base Center. The structural manipulations on β-CD were made using the CAChe library[29] on PC-Computer. The study of compound **3** was performed by applying a general procedure of multiconformational search with the MM3 force field.[30] The potential energy variation (ΔE) depending on the variation of the dihedral angles (defined between the TTF and cyclodextrin moieties) is recorded with rotational increments of 15°. The minimum value of ΔE is chosen according to the curve scribing. The analysis was developed taking into account all the exocyclic single bonds in the compound **3**. Then, the docking of the guest (1-adamantanol) with respect to the locked β-CD unit has been performed using three dummy atoms, one centrally placed in the inner cavity of the cyclodextrin ring and the two others in opposite sites towards the guest (Fig. 3). Two parameters, i.e., the host/guest distance and the orientation of 1-adamantanol inside the cyclodextrin cavity, are submitted to systematic variations (0.1 Å for the distance, 10° for the dihedral), the energy being evaluated by MM3. The resulting conformations are minimized at each step of the docking simulation, thus allowing the remaining intermolecular variables to be taken into account.

Acknowledgements

Financial supports from the CNRS, Ministère de l'Education et de la Recherche (grant for C.R.), University of Angers and University of Dunkerque are gratefully acknowledged.

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