Monatsh Chem 139, 949–952 (2008)
DOI 10.1007/s00706-007-0850-8
Printed in The Netherlands

Monatshefte für Chemie
Chemical Monthly

A facile one-pot synthesis and the crystal structure of a molecular clip derived from diphenylglycoluril

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Received 14 August 2007; Accepted 8 November 2007; Published online 26 June 2008

Abstract A facile procedure for the one-pot synthesis of a clip molecule *via* condensation of diphenylglycoluril, paraformaldehyde, and 4-dimethoxybenzene in the presence of methanesulfonic acid is described. The advantages of this method are mild conditions, single product formation and good yield. Especially, the procedure of the product purification is more simple and convenient. In addition, the clip molecule is characterized by X-ray crystal structure analysis, which shows different weak interactions forces compared to the structure reported previously.

Keywords One-pot synthesis; Crystal structure; Molecular clip; Diphenylglycoluril.

Introduction

In 1987, *Nolte et al*. synthesized some organic receptors based on diphenylglycoluril commonly referred to as ''molecular clips'' [1], such as **4**. This molecule possesses a well-defined and rigid U-shaped cavity, which is formed by the glycoluril framework and two aromatic side walls. With its preorganized cleft, it is a good receptor for a 1,3-dihydroxybenzene guest molecule in a chloroform solution through hydrogen bond, $\pi-\pi$ stacking interactions, and a so-called ''cavity effect'' [2–5]. In addition, in the solid state, the molecule can form head-to-head dimeric structures, in which the cavity of one molecule is filled by one of the side-walls of its dimeric partner and *vice-versa* [6–9]. This property was applied to create well-defined nanosized materials [10–12]. Herein, we report a facile procedure for the synthesis of this molecule and different interactions forces in its crystal structure.

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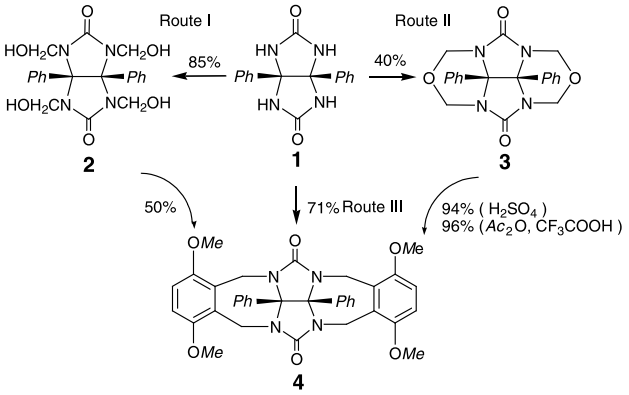
Results and discussion

In our research, we need **4** as an intermediate to synthesize other functional receptors. There are two synthesis routes used to synthesize the compound. Route I (Scheme 1, $\mathbf{1} \rightarrow \mathbf{2} \rightarrow \mathbf{4}$): diphenylglycoluril **1** [13] was treated with paraformaldehyde and NaOH in *DMSO* to yield tetrakis(hydroxymethyl) derivative **2** (85%) [14], the latter compound was reacted with an excess of 1,4-dimethyoxybenzene in 1,2-dichloroethane using 4-methylbenzenesulfonic acid as catalyst and gave **4** in 50% yields [1]. Route II (Scheme 1, $\mathbf{1} \rightarrow \mathbf{3} \rightarrow \mathbf{4}$): as preparation of **2**, the reaction mixture was adjusted to *pH* 1 with concentrated HCl, **1** was transformed to intermediate cycloether **3** (40%) [13], which reacted with an excess of 1,4-dimethoxybenzene in H_2SO_4 or a mixture of acetic anhydride and trifluoroacetic acid



Scheme 1

to furnish **4** in 94, 96% yields [14]. As two steps involved acidic conditions, we hoped to identify an appropriate acid which would allow to perform the whole procedure as a one-pot synthesis (Scheme 1). In our study, several acid systems (H_2SO_4, HCl, CF_3COOH, CF_3SO_3H, CH_3SO_3H, and 4-methylbenzenesulfonic acid) were tested and methanesulfonic acid was proven to be most effective for the reaction. In the presence of methanesulfonic acid, we can obtain **4** in good yield (71%) (see experiment section). In contrast to the previously reported procedures our method does not require the purification of intermediates. Moreover, the advantages of this method are mild conditions, single product formation, and good yield. Especially, the procedure of the product purification is more simple and convenient.

In addition, we describe here the solid structure of a new polymorph of **4** and compare it with *Nolte*'s structure. The colorless single crystal of **4** was cultured from a solution of chloroform by slow evaporation at room temperature. The X-ray crystal structure of **4** is shown in Fig. 1 with 30% thermal ellipsoids probability. The molecule possesses a C_2 symmetry axis. The bond distances and bond angles of the title compound are in good agreement with the corresponding values obtained in case of related glycoluril derivatives [3]. The angle between the mean planes defined by the fused 2-imidazolidone rings is 70.2° and the distance between the two carbonyl oxygens amounts to 5.51 Å. The dihedral angle between the aromatic ring sides is 40.1° with the centers of the benzene rings 6.68 Å apart.

In the structure obtained by *Nolte*, the molecules are arranged as consecutive head-to-head dimers (Fig. 2a). Sheets of clips giving an interwoven network (Fig. 2b) which is stabilized by $\pi-\pi$ stacking interactions between the clip layers [7].

Interestingly, we cannot find head-to-head dimers in the crystal structure. In Fig. 3a, there are no direction-specific interactions between the clipped molecules. Instead, tail-to-tail dimers are formed, which are linked by intermolecular hydrogen bond (Fig. 3b). The intermolecular hydrogen bonds between atoms are as follows: C(16)–H(16)···O(3) has length 3.332(5) Å and an angle of 157.4°, with symmetry code $-x$, $1-y$, $-z$.

In addition, $\pi-\pi$ stacking interactions are also not observed between the clip layers. These layers are linked into an interwoven network by weak inter-

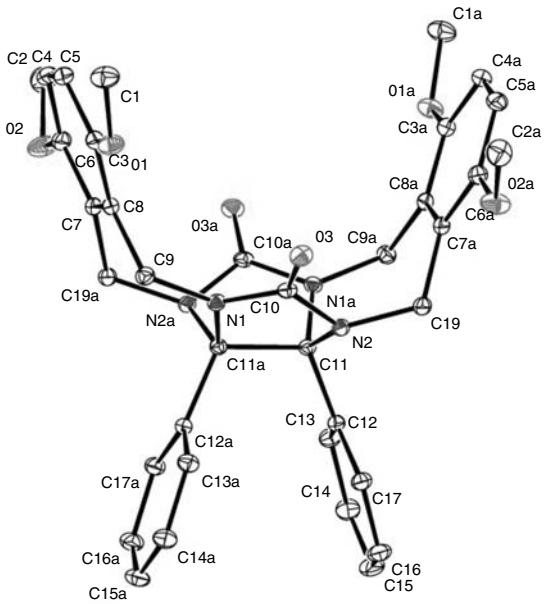


Fig. 1 The molecular structure of **4**

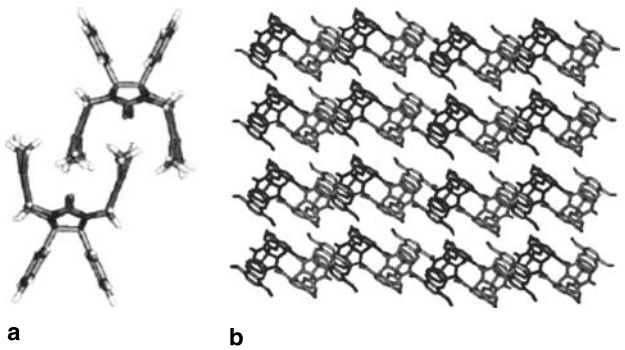


Fig. 2 Part of the crystal structure of *Nolte*'s

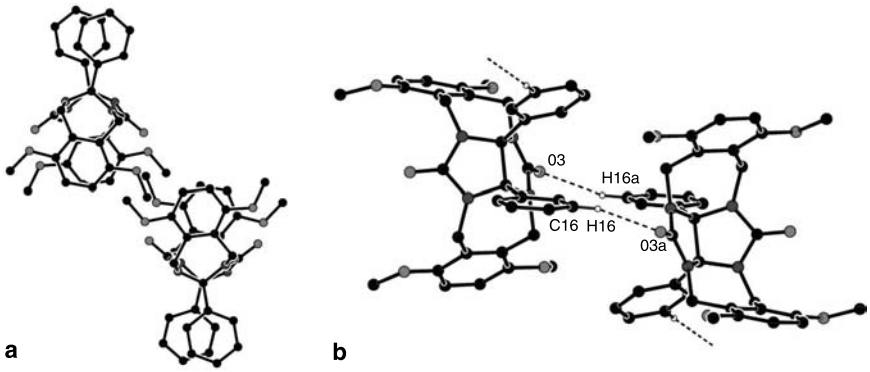


Fig. 3 Part of the crystal structure of **4**

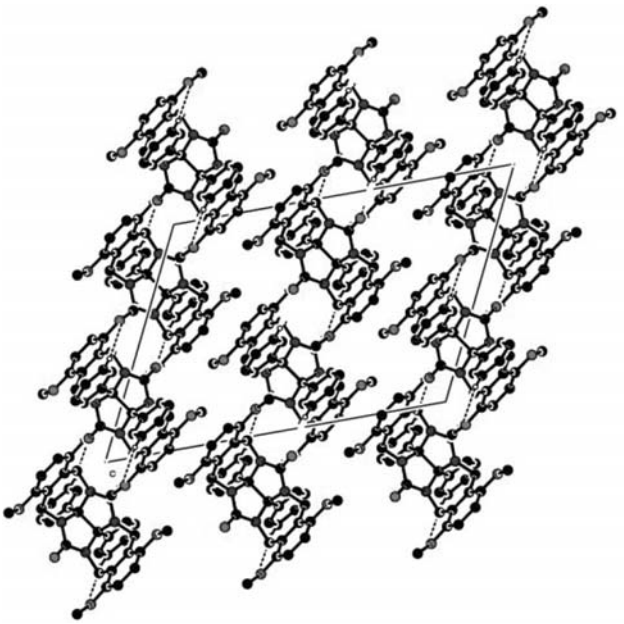


Fig. 4 Packing diagram of **4** viewed along the y-axis

molecular C–H$\cdots\pi$ interactions (Fig. 4). This interaction, with the proton shared between C(1) and the π-electron system of the benzene ring C(12)–C(17), has an H$\cdots\pi$ distance of 3.04 Å and an angle of 167.8°, with symmetry code $-1/2+x, 3/2-y, -1/2+z$.

Experimental

General

The melting point was determined with XT4A micromelting point apparatus. The ^{1}H NMR was recorded on a Mercury Plus-400 spectrometer with TMS as internal reference and $CDCl_3$ as solvent. MS were obtained with Finnigan Trace MS instrument using EI method.

5,9,14,18-Tetrahydro-1,4,10,13-tetramethoxy-19,20-diphenyl-7H,16H-6,17:8,15-dimethanodibenzo[e,l][1,3,8,10]tetraazacyclotetradecine-7,16-dione (**4**)

A mixture of 2.94 g (diphenylglycoluril 10.0 mmol), 1.5 g (paraformaldehyde 50.0 mmol), and 1.3 cm^3 (methanesulfonic acid 20.0 mmol) in 35 cm^3 1,2-dichloroethane was heated at reflux for 3 h under a *Soxhlet* apparatus filled with molecular sieves (4 Å). After cooling, 2.76 g (1,4-dimethoxybenzene 20.0 mmol) was added and reflux was continued for 20 h. The reaction mixture was stored overnight at −6°C, then the precipitate was filtered off, washed with 2×20 cm^3 *Et*O*Ac*, and dried in vacuo. Compound **4** (4.38 g, 71%) was obtained as a white solid. Mp >300°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.08$ (s, 10H, *Ar*H), 6.48 (s, 4H, *Ar*H), 5.60 (d, $J=16.0$ Hz, 4H, NCH$_2$*Ar*), 3.76 (d, $J=16.0$ Hz, 4H, NCH$_2$*Ar*), 3.72 (s, 12H, O*Me*); EI-MS: $m/z=619$ (26, $[M+1]^+$), 151 (100).

X-Ray crystallography

A single crystal of approximate dimensions 0.30 mm × 0.20 mm × 0.20 mm was used. X-Ray diffraction data were collected at 292(2) K on a Bruker Smart-1000CCD diffractometer, using graphite monochromatized Mo Kα radiation ($\lambda=0.71073$ Å). The crystal belongs to monoclinic, space group $C2/c$ with $a=19.677(2)$, $b=12.2903(15)$, $c=13.9591(17)$Å, $\beta=116.232(2)$, $V=3028.1(6)$ Å^3, $Z=4$, $D_c=1.357$ g/cm^3, $\mu(\mathrm{MoK}_\alpha)=0.094$ mm^{-1}, $F(000)=1304$. A total of 3126 reflections were collected in the range of $2.02<\theta<27.00°$ at room temperature, and 8778 were independent ($R_{\mathrm{int}}=0.0291$), of which 3291 observed reflections with $I>2\sigma(I)$ were used in the structure determination and refinements. The structure was solved by direct methods using the program SHELXS-97 [15]. Refinements were done by the full-matrix least-squares on F^2 using SHELXL-97 [16]. Nonhydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms were located from a difference *Fourier* map and refined without restrains. A full-matrix least-squares refinement gave the final $R=0.0529$, $wR=0.1277$. CCDC-626012 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html

or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44(0)1223-336033; e-mail: deposit@ccdc.cam.ac.uk.

Acknowledgements

The authors are grateful to Prof. *An-Xin Wu* for helpful discussions. This study was financially supported by National Natural Science Foundation (No. 20672042), Innovative Team and Key Project (No. Z2006zd02) of Huangshi Institute of Technology.

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