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Solution conformations of novel redox-active cyclophane based on biindolizinequinoxaline

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Abstract

A complete study of the conformational behavior of cyclopentadecaphane by DNMR and theoretical methods demonstrates that: (a) the macrocycle adopts *syn*-orientation of indolizine fragments; (b) internal rotation around the bonds between indolizine and quinoxaline moieties produces two strictly different structures in solution: in dominant non-symmetrical form (ca. 67%) the halves of the macrocycle are not equivalent while in the minor symmetrical form (ca. 33%) they can be superimposed by rotation.

Keywords: DNMR; GIAO–DFT chemical shifts; 2D NMR; 3D structure; Macrocycle; Indolizinequinoxaline

1. Introduction

Biological systems use the interplay of redox and molecular recognition to regulate a wide variety of processes and transformations [1a]. Redox-active heterocycles are important to materials science and to biochemistry. Some of redox-active macrocyclic compounds have been proposed as candidates for ion transport [1b]. Therefore in recent years, there is a considerable interest in the creation of such organic based molecular devices that have the potential to function as information storage/switching systems in molecular scale computers and other applications [2].

To this end cyclophanes based on biindolizinquinoxaline moieties linked through C3′—C3′* (biindolizine linkage) bond and by oxypentane spacer seem to be a perspective redox-active "host" (Scheme 1): the combination of the electron-rich aromatic π-systems with electron-rich biindolizines leads to possibilities of π–π-interactions with potential guests such as aromatic compounds [3]; the presence of the crown ether moiety allows to utilize the central feature of the crown ethers – their ability to form stable and selective complexes with various inorganic and organic cations [4].

Moreover, the indolizine, quinoxaline and crown ether fragments play an important role in synthetic, therapeutic, and bioorganic chemistry. The quinoxaline derivatives show antibacterial, antiviral, anticancer, antifungal, antihelmintic, insecticidal activity [5]. Indolizines demonstrate antifungal, antimycobacterial, antiherpes and antineociceptive properties [6]. Crown ethers are found to be toxic in prokaryotic and eukaryotic cellular systems, which led to further studies on their potential for being developed as antimicrobial agents [4,7].

Over recent years there has been a trend in biochemistry towards the synthesis of extended molecular entities that are multi-component. Moreover, linked preorganized systems are of considerable intrinsic interest since they can give rise to new derivatives whose properties may be more than the "sum of the parts" [1b,7a,8].

The outcome of the operation of these systems in their use as molecular devices and/or as biologically active recognition agents in resulting supramolecular systems depends strongly on their 3D structure. Therefore the development of structure/property relationships

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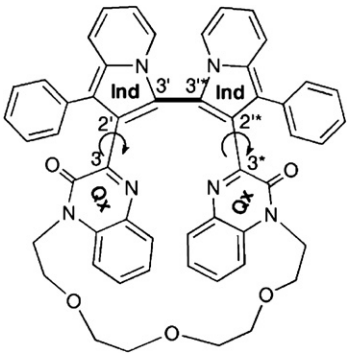

Scheme 1.

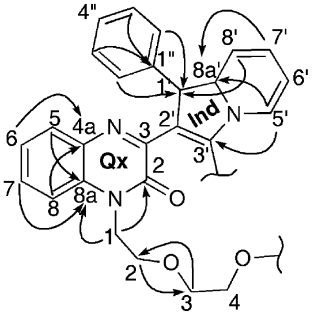

Fig. 1. The principal HMBC correlations for **1** (from protons to carbons): data only for the half of the molecule are shown for clarity.

and the knowledge of conformations and dynamics of these cyclophanes in solution is of utmost important [2e,2f,9].

Recently we reported the synthesis of diastereoisomeric triethylenglycol-bridged biindolizinequinoxaline **1** (Scheme 1) [10]. The product proved to have a reversible redox property. The chemical and isomeric structure of **1** was investigated in solid state and in solution by X-ray and NMR methods. In addition, according to our preliminary experiments at a room temperature there is extensive coalescence of signals in ^{1}H NMR spectra of the macrocycle that may be ascribed to conformational equilibrium. In this paper we present our results of an investigation into conformational structure and dynamics of **1** in solution by a variety of experimental and theoretical NMR methods.

2. Experimental

2.1. Synthesis of compounds

2.1.1. 21,31-Diphenyl-12,42-dioxa-7,10,13-trioxa-1,4(3,1)-diquinoxaline-2(2,3),3(3,2)-diindolizineacycledeaphane (*1*)

Compound **1** was prepared according to Ref. [10]. ^{1}H NMR (DMF, 600 MHz, 50 °C): $\delta = 3.40$ and 3.54 (4H, m, CH_2-2), 3.42 (4H, m, CH_2-4), 3.43 and 3.49 (4H, m, CH_2-3), 3.83 and 4.02 (4H, m, CH_2-1), 6.83 (2H, dd, $J = 6.9$, 6.7 Hz, H-6′), 7.02 (2H, dd, $J = 9.4$, 6.6 Hz, H-7′), 7.14 (2H, dd, $J = 7.4$, 7.0 Hz, H-4″), 7.20 (2H, ddd, $J = 8.0$, 5.7, 2.3 Hz, H-6), 7.25 (4H, dd, $J = 7.8$, 7.6 Hz, H-3″/5″), 7.30 (2H, d, $J = 7.9$ Hz, H-5), 7.37 (4H, d, $J = 7.6$ Hz, H-2″/6″), 7.51 (4H, m, H-7, H-8), 7.72 (2H, d, $J = 8.7$ Hz, H-5′, H-8′); ^{13}C NMR (DMF, 150.86 MHz, 50 °C): $\delta = 42.28$ (CH_2-1), 67.62 (CH_2-2), 70.53 (CH_2-4), 70.70 (CH_2-3), 112.43 (C-6′), 114.69 (C-8), 115.26 (C-3′), 115.44 (C-1′), 118.46 (C-8′), 120.15 (C-7′), 123.30 (C-6), 125.11 (C-2′), 125.15 (C-5′), 126.10 (C-4′), 128.70 (C-3″/5″), 129.89 (C-2″/6″), 129.99 (C-5), 130.52 (C-7), 131.42 (C-8a′), 133.52 (C-4a), 134.06 (C-8a), 136.01 (C-1″), 147.98 (C-3), 154.24 (C-2); $m/z = (830)M^+$; IR, ν, cm^{-1} (neat) (Vector-22 (Bruker)): 704, 729, 762, 1103, 1128, 1159, 1251, 1281, 1346, 1366, 1454, 1486, 1524, 1583, 1601, 1649, 2857, 2922. $C_{52}H_{44}N_6O_5$.

2.2. NMR spectroscopy

NMR experiments were carried out with a Bruker AVANCE-600 spectrometer (14.1 T) equipped with a pulsed gradient unit capable of producing magnetic field pulse gradients in the z-direction of 56 G cm^{-1}. All spectra were acquired in a 5-mm inverse probehead working at 600.000 MHz in ^{1}H and 150.864 MHz in ^{13}C experiments. Chemical shifts are reported on the δ (ppm) scale and are relative to the residual ^{1}H and ^{13}C signal of DMF-d_7. A complete assignment of **1** was accomplished by DEPT, 2D COSY-gp, 2D HSQC-gp, 2D HMBC-gp experiments [11], using standard Bruker pulse programs (related 1D and 2D NMR spectra can be obtained in Supporting materials). The 90°-pulse widths were 7 μs and 12 μs for ^{1}H and ^{13}C, respectively. For 2D COSY-gp: d_1(relaxation delay) = 1.5 s ($T = 333$ K) and $d_1 = 1$ s ($T = 213$ K). For 2D HSQC-gp: $d_1 = 2.5$ s ($T = 333$ K) and $d_1 = 1$ s ($T = 213$ K), optimized on $^1J_{CH} = 145$ Hz. For 2D HMBC-gp: $d_1 = 2.5$ s, optimized on $^1J_{CH} = 145$ Hz and $^nJ_{CH} = 9$ Hz. For 2D NOESY-gp: $d_1 = 3$ s, mixing time 600 ms and ROESY-gp: spin-lock time 600 ms.

For DNMR spectroscopy, a standard unit calibrated using a methanol reference controlled the probe temperature; the samples were allowed to equilibrate for 15 min at each temperature before recording spectra.

Line shape analysis of signals broadened by chemical exchange was carried out by WinDNMR v.7.1.6 program [12] on Pentium 4 computer. Activation parameters were calculated by Eyring equation [13].

Molecular mechanics (employing the MM2 force field) were performed with CS Chem3D Ultra 6.0 (CambridgeSoftCorp.). Chemical shifts were determined within the DFT framework using a hybrid exchange-correlation functional, B3LYP, at the 6-31G(d) level as implemented in Gaussian 98 [14]. Full geometry optimizations were done at the ab initio RHF/6-31G level. All data were referred to TMS (^{1}H and ^{13}C) chemical shifts that were calculated at the same conditions. All calculations were run on a Pentium 4 (CPU 2.80 GHz 512 MB RAM) computer.

3. Results and discussion

The complete structure elucidation of compound **1** was carried out by variety of correlation NMR methods (2D