The Effect of Intramolecular-Hydrogen Bonds in The Synthesis of Novel Imidates From a 13-Membered Dioxadithia Crown Ether Diester

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Received May 9, 2003

The synthesis and structural properties of three novel imidates, 11,13-bis-(2-amino-ethylimino)-1,10-dioxa-4,7-dithiacyclotridecane (**2**), 11,13-bis-(3-aminopropylimino)-1,10-dioxa-4,7-dithiacyclotridecane, (**3**) and 2,11-dioxa-5,8-dithia-13,16,19,22-tetraazabicyclo[10.10.1]tricosa-1(22),12-diene, (**4**) have been described. These compounds were synthesized by treating 1,10-dioxa-4,7-dithiacyclotridecane-11,13-diester (**1**) with the appropriate diamine under N_2 and their structures have been characterised by elemental analyses, ^{1}H- and ^{13}C-nmr, ir, and mass spectral studies. Elemental analyses and spectroscopic data support the proposed imidate structures. In addition, total energy and heat of formation (Figure 2) calculated for imidates **2a-4a** and **2b-4b** by the semiempirical AM1 calculations have shown that imidates **2b-4b** having intramolecular hydrogen bonds are more stable (5-10 kcal/mol) than compounds **2a-4a**.

Introduction.

In recent years, synthetic chemists have generally focused on syntheses of new organic ligands mimicking protein-metal binding sites in biological systems [1-9] to use as therapeutic agents [10] or catalytic reagents [11] and to study host-guest interactions [12]. At the same time, considerable effort has been performed in developing reliable inexpensive synthetic routes to such metal containing compounds. Furthermore, attention has also been directed towards determination of the parameters that affect complex stability in terms of thermodynamic and kinetic data [13-15].

The crown ethers and their metal complexes have proved to be useful in the area of selective ion-macrocycle interaction since they have a high degree of cation selectivity [13-15]. Various changes have been made to the basic crown ether structure in an attempt to enhance the selectivity of these ligands and the stability of complexes formed with both metal and organic cations [16-20]. Some of these modifications involve the substitution of the ligand polyether oxygen donor atoms by sulphur or nitrogen atoms [11,16-20]. In addition, dinucleating macrocycles have been synthesized by linking together chelating acyclic subunits [21-23] or by functionalising a macrocyclic structure by attaching side chains [24]. It has been reported that the derivatized macrocyclic systems exhibited the characteristics of mono- and dinuclear complexes such as catalysis and molecular recognition. More recently, it has been reported that azamacrocycles and their metal complexes possess anti-HIV activity [25]. Furthermore, various mononuclear metal complexes of Schiff base ligands modified with benzo-15-crown-5 have been shown to possess enzyme-like activities [6-9]. Some of the macrocycles have also found application in the removal of toxic metal ions from waste water [26].

We describe here the preparation of three novel ligands, 11,13-bis-(2-aminoethylimino)-1,10-dioxa-4,7-dithia-cyclotridecane, (**2**), 11,13-bis-(3-aminopropylimino)-1,10-dioxa-4,7-dithiacyclotridecane, (**3**) and 2,11-dioxa-5,8-dithia-13,16,19,22-tetraazabicyclo[10.10.1]tricosa-1(22),12-diene, (**4**), Characterization of compounds **2-4** was accomplished using elemental analyses, ms, nmr, and ir spectra. In addition, total energy and heat of formation (Figure 2) calculated for the imidates **2a-4a** and **2b-4b** by semiempirical AM1 calculations show that imidates **2b-4b** possessing intramolecular hydrogen bonds are more stable (5-10 kcal/mol) than compounds **2a-4a**.

Results.

We initially aimed to interact a diester of the dioxadithia crown ether moiety [27] with several aliphatic amines to produce novel imidates. The synthetic strategy depends on the cyclocondensation between bis amines and a diester, to give the corresponding condensation products. The cyclocondensation reactions are known to occur either in the absence or in the presence of metal ions [28-29]. The latter can serve to direct the condensation preferentially to cyclic rather than polymeric products and to stabilize the macrocycles once formed. The reactions proceed to give "1+1 or 2+2" macrocycles depending, together with other factors, on the size of the template ion and the chain length of both of the diamines and the bis-diketones.

The synthetic routes to novel monomacrocycles fused to two aliphatic bis diamine units (**2**, **3**) or bicycles fused to one aliphatic tetramine unit (**4**) are outlined in Scheme 1. 1,10-Dioxa-4,7-dithiacyclotridecane-11,13-diester (**1**) was prepared under a nitrogen atmosphere by the reaction of a dichloromethane solution of malonyl dichloride with 1,8-dihydroxy-3,6-dithiaoctane. 11,13-Bis-(2-aminoethylim-

ino)-1,10-dioxa-4,7-dithiacyclotridecane (**2**), 11,13-bis-(3-aminopropylimino)-1,10-dioxa-4,7-dithiacyclotridecane (**3**) and 2,11-dioxa-5,8-dithia-13,16,19,22-tetraazabicyclo[10.10.1]tricosa-1(22),12-diene (**4**) were prepared by a similar reaction in separate containers under a nitrogen atmosphere by the reaction of a dioxan solution of either 1,2-ethylenediamine, 1,3-diaminopropane or triethylentetramine with **1** (Scheme 1). The structural formulae of the novel imidates (**2-4**) were verified by elemental analyses and [^1]H- and [^13]C-nmr, ir and mass spectral data.

proposed formula (Scheme 1). Analysis by [FAB(positive)] MS data indicated ions at m/z 377.1 (14 %), [M+CH$_2$CH$_2$NH]$^+$ for **2**, m/z 361 (15 %), [M-1]$^+$ for **3** and m/z 360.5 (15 %), M$^+$ for **4**. All these mass spectral data support the formation of the synthesized imidates.

In the ir spectra the -C=O bands at about 1754, 1730 cm^{-1} in the IR spectrum of **1** were shifted to lower frequencies 100 cm^{-1} for imidates **2-4** showing the formation of the C=N units. All these changes in the frequencies have been compared with the vibration modes of **1**. In

Scheme 1
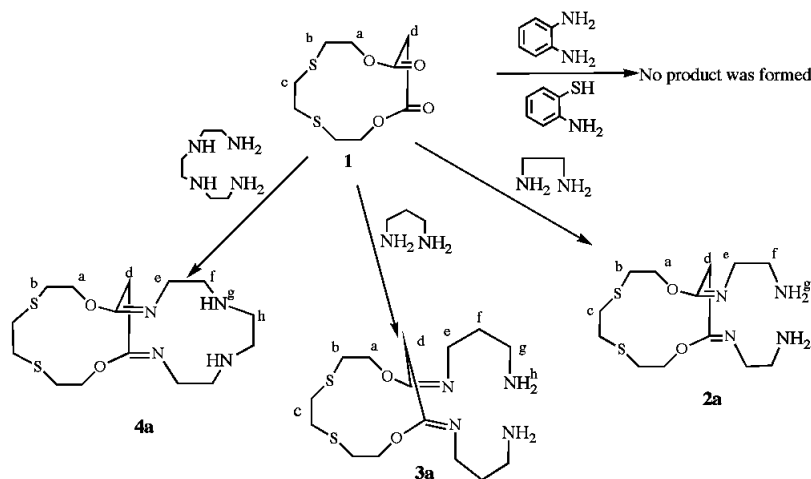
In the [^1]H-nmr spectrum (DMSO-d$_6$,) of **2**, a multiplet was observed at 2.55-2.59 ppm (b, S-CH$_2$-, e, C=N-CH$_2$-, 8H), a singlet at 3.02 ppm (c, S-CH$_2$-CH$_2$-S, 4H), a broad singlet at 3.11 ppm (f, -CH$_2$-N-, 4H), a triplet at 3.56 ppm (a, -OCH$_2$-, 4H), a singlet at 2.6 ppm (d, CH$_2$-C=N, 2H) and a broad singlet at 8.23 ppm (g, NH$_2$ 4H) corresponding to the resonances of aliphatic protons, respectively. The seven resonances (see experimental section) observed in the [^13]C- nmr spectrum of **2** are also consistent with the proposed formula (Scheme 1).

In the [^1]H- nmr. (DMSO-d$_6$,) spectrum of 3, a broad singlet was observed at 1.52 ppm (e, CH$_2$-N=, 4H), a multiplet at 2.53 ppm (f, S-CH$_2$-, 4H), a multiplet at 3.0-3.4 ppm (b+c+d+g, 14H), a triplet at 3.6 ppm (a, O-CH$_2$-, 4H), and a broad singlet at 8.07 ppm (-NH$_2$, 4H). The eight resonances (see experimental section) observed in the [^13]C-nmr spectrum of **2** are also consistent with the proposed formula (Scheme 1).

In the [^1]H- nmr (DMSO-d$_6$,) spectrum of **4**, a multiplet was observed at 2.2-2.60 ppm (b+c+f+h, 16H), a singlet at 2.70 ppm (d, CH$_2$-C=N, 2H), a broad singlet at 3.0-3.47 ppm (a+e, 8H), a broad singlet at 8.06 ppm (-NH, 2H). The eight resonances (see experimental section) observed in the [^13]C- NMR spectrum of **4** are also consistent with the

general, the new compounds exhibited very similar ir spectral features indirectly showing evidence that the imidates have similar structures.

Compound **1** is expected to give amides by treatment with amines since it is an ester. However, it is clear from the present study that the reactivity of **1** towards amines depends on the basicity of the individual amine compound. Compound **1** did not react with aromatic amines such as phenylenediamine or *o*-aminothiophenol in the presence of various solvents such as ethanol, dioxane and acetonitrile at room temperature nor under reflux. This compound behaves like as a ketone and produces Schiff base like imidates in dioxane on a water-ice bath when treated with aliphatic amines. On the other hand, the proton resonances in the nmr spectra belonging to –NH$_2$ and –NH groups of the produced imidates were observed at approximately 8 ppm. This surprising shift for the imidates can be attributed to strong intramolecular hydrogen bonds [30-33] (Figure 1). Unexpected behaviours were also observed in the ir spectra for **2** and **3**. The symmetric and antisymmetric vibrations which are specific for -NH$_2$ groups were seen as a broad peak with a shoulder at 3300 cm^{-1} instead of a doublet. This is also consistent with the formation of intramolecular hydrogen bonding. In general, the solubility of
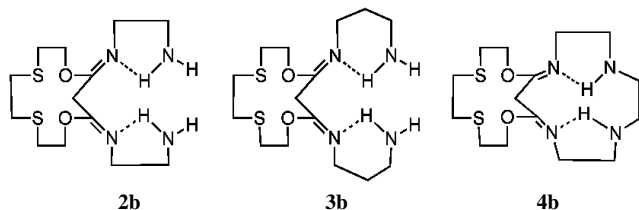
2b   **3b**   **4b**

Figure 1.   Proposed structure for the intramolecular hydrogen-bonded Schiff bases.

produced imidates **2-4** in common organic solvents is pretty low. In contrast, they are highly soluble in dimethylsulfoxide or water, thus indicating their potential to form strong intramolecular hydrogen bonds.

Total energy and heat of formation (Figure 2) were calculated for the imidates 2a-4a and 2b-4b by semiempirical AM1 calculations [34] show that imidates 2b-4b possessing intramolecular hydrogen bonds are more stable (5-10 kcal/mol) than compounds 2a-4a. The mechanism imidates formation is thought to involve an intermediate in which one of the amine nitrogen atoms of each amine molecule attacks one of the electropositive carbonyl carbons. One of the two hydrogen atoms at the free ends of each diamine molecule forms a hydrogen bond with the oxygen atom of the macrocycle and the other hydrogen with the nitrogen attached to the carbonyl carbon (Scheme 2). It can be assumed that this interaction prevents the ester compound from undergoing amminolysis to form an amide.

In conclusion, three new imidate ligands, which are fused to a cyclic dione at the -C=O position were accomplished. The structures proposed for these new compounds, 2-4 are consistent with the data obtained from their elemental analyses, ir , ^{1}H-, ^{13}C-nmr and mass spectrometry.

EXPERIMENTAL

Instrumentation.

Melting points were determined in open capillaries and are corrected; ^{1}H- and ^{13}C-nmr spectra were recorded on a Varian Gemini 200 spectrometer using DMSO-d_6 as solvents. Chemical shifts ( ) are reported in ppm relative to Me$_4$Si, using the solvent signal as
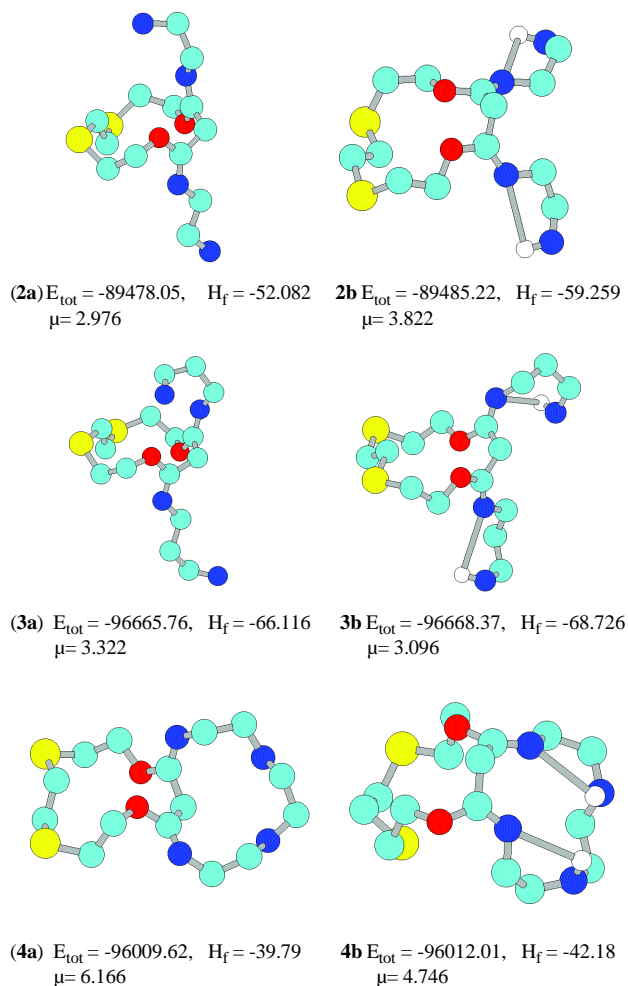

(**2a**) E_{tot} = -89478.05, H_f = -52.082   **2b** E_{tot} = -89485.22, H_f = -59.259
        μ= 2.976 μ= 3.822

(**3a**) E_{tot} = -96665.76, H_f = -66.116   **3b** E_{tot} = -96668.37, H_f = -68.726
          μ= 3.322 μ= 3.096

(**4a**) E_{tot} = -96009.62, H_f = -39.79   **4b** E_{tot} = -96012.01, H_f = -42.18
          μ= 6.166 μ= 4.746

Figure 2:The lowest energy conformations byAM1 optimized geometries of non-hidrogen bonded Schiff bases (**a**) and intramolecular hidrogen-bonded Schiff bases (**b**) and its E_{tot}, H_f energies (kcal/mol) and dipole moments (Debye).

internal reference. Ir spectra were recorded on a Matson 1000 Model FTIR spectrophotometer in KBr pellets. C, H and N contents, mass spectra [FAB(positive)] were recorded at The Scientific and Technical Research Council of Turkey (Gebze, Turkey). 1,4-Dioxane was distilled from sodium; Dimethylsulfoxide (DMSO), aliphatic amines, and dichloromethane were distilled from calcium hydride; and CHCl$_3$ was distilled from CaCl$_2$.

Scheme 2
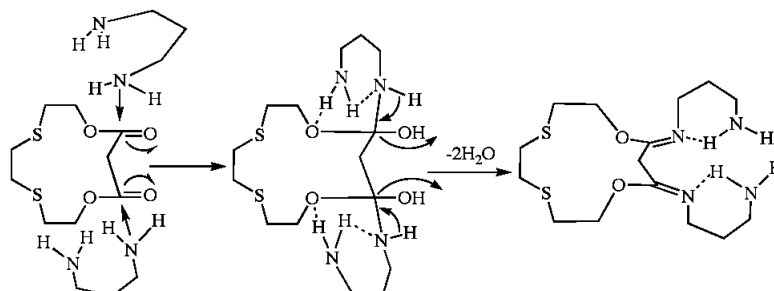
Chromatographic separations were performed on silica gel 60 (230-400 mesh, 60 Å) using the indicated solvents. 1,10-Dioxa-4,7-dithiacyclotridecane-11,13-diester, (**1**) was prepared according to the previous report [12].

Geometry optimization of the imidates was performed using the molecular mechanics MM+ module and AM1 semiempirical calculations in the HyperChem 6.03 molecular modeling program package [14]. Molecular mechanics used the MM+ as a classical Newtonian calculation method which, in the energy minimization procedure, includes bond lengths, bond angles, torsion angles, and noncovalent interactions. Energy minimization used the Smart Minimizer, which is a combination of methods, starting with the Steepest Descent Method, followed by the Fletcher-Reeves and Block-diagonal Newton-Raphson methods, and ending with the accurate Polak-Ribiere method. The semiempirical AM1 calculations used MOPAC/AM1 version 6.03, including electronic properties, optimized geometries, total energy, dipole moment and heat of formation as known SCF method [14].

11,13-Bis-(2-aminoethylimino)-1,10-dioxa-4,7-dithiacyclotridecane (2).

To a vigorously stirred **1** (2.5 g, 10 mmol) in dioxane (20 mL), a solution of 1,2-ethylenediamine, (1.2 g, 20 mmol) in dioxane (5 mL) was added at 0 °C over ca. 10 minutes. After stirring for 48 hour at room temperature, the precipitated product was collected by filtration. A pale-pink solid material was recrystallized, from DMSO-MeOH, collected by filtration, washed with cold MeOH, $(CH_3)_2CO$ and EtOAc, successively, and dried in vacuo over P_2O_5. Product was isolated as a pale pink solid 1.67 g (50%), mp 154-155°; ^{1}H-nmr (deuteriodimethylsulfoxide): 2.55-2.59 (m., 8H, b, $S-CH_2-$ e, $C=N-CH_2-$) 3.02 (s., 4H, c, $S-CH_2-CH_2-S$), 3.11 (b.s., 4H, f, $-CH_2-N-$), 3.56 (t., 4H, a, $-OCH_2-$), 2.6 (s., 2H, d, $CH_2-C=N$), 8.23 (b.s., 4H, g, NH_2, deuterium oxide-exchangeable); ^{13}C-nmr (deuteriodimethylsulfoxide): 31.6 (d, $CH_2-C=N$), 32.1 (b, CH_2-S), 33.7 (c, $S-CH_2$), 40.6 (e, $CH_2-C=N$), 43.1 (f, CH_2-NH), 60.9 (a, $-OCH_2-$) 166.5 (C=N); ms: [FAB(positive)] m/z 377.1(10.0), 317.6(15.1), 189.2(100); ir.(KBr, cm^{-1}) br. NH_2 3287, C=N 1653, C-S 1344.

Anal. Calcd. for $C_{13}H_{26}N_4O_2S_2$: C, 46.7; H, 7.8; N, 16.8. Found: C, 46.8; H, 7.6; N, 16.6.

11,13-Bis-(3-aminopropylimino)-1,10-dioxa-4,7-dithiacyclotridecane (3).

To a vigorously stirred solution of **1** (2.5 g, 10 mmol) in dioxane (20 mL), a solution of 1,3-diaminopropane (1.48 g, 20 mmol) in dioxane (5 mL) was added at 0 °C over ca. 10 minutes. After stirring for 72 hour at room temperature, the precipitated product was collected by filtration. A white solid product was recrystallized, collected by filtration, washed with Et_2O and dried in vacuo over P_2O_5. Product was isolated as a white solid 1.98 g (55%), mp 203-205°; ^{1}H-nmr (deuteriodimethylsulfoxide): 1.52 (b.s., 4H, e, $CH_2-N=$), 2.53 (m, 4H, f, $S-CH_2-$), 3.0-3.4(m, 14H, b+c+d+g) 3.6 (4H, a, $O-CH_2-$), 8.07 (b.s., 4H, $-NH_2$, deuterium oxide-exchangeable); ^{13}C-nmr (deuteriodimethylsulfoxide): 31.9 (e, $CH_2-C=N$), 36.1 (b, CH_2-S), 36.4 (d, $-OCH_2-$) 38.1 (c, $S-CH_2$), 40.1 (g, $-CH_2-NH_2$), 43.4 (f, $-CH_2$), 61.5 (a, $O-CH_2-$), 166.75 (C=N); ms: [FAB(positive)] m/z 361(14), 359.1(64), 232(35), 217.1(78), 156.9(100); ir (KBr, cm^{-1}) br. NH_2 3291, C=N 1634, C-S 1343.

Anal. Calcd. for $C_{15}H_{30}N_4O_2S_2$: C, 49.7; H, 8.3; N, 15.4. Found: C, 49.8; H, 8.4; N, 15.4.

2,11-Dioxa-5,8-dithia-13,16,19,22-tetraazabicyclo[10.10.1]tricosa-1(22),12-diene, (4).

To a vigorously stirred solution of **1** (2.5 g, 10 mmol) in dioxane (20 mL), a solution of triethylenetetramine (7.20 g, 20 mmol) in dioxane (5 mL) was added at 0 °C over ca. 10 minutes. The mixture was stirred for 48 hour at room temperature, then refluxed for 16 h. The reaction mixture was evaporated and the oily material was stirred in Et_2O and decanted. A yellow oily product was obtained. The resultant residue was purified by column chromatography on silica using 20% EtOAc/n-hexane. Product was isolated as a pale-yellow oil 2.52 g (70%); ^{1}H-nmr (deuteriodimethylsulfoxide): 2.2-2.60 (m., 16H, b+c+f+h), 2.70 (s., 2H, d, $CH_2-C=N$), 3.0-3.47 (b.s., 8H, a+e), 8.06 (b.s., 2H, -NH, deuterium oxide-exchangeable); ^{13}C-nmr (deuteriodimethylsulfoxide): 31.6 (b, CH_2-S), 33.74 (c, $S-CH_2$), 38.1 (d, $CH_2-C=N$), 38.7(e, $CH_2-C=N$), 48.55 (f, CH_2-NH), 55.95 (h, CH_2-NH), 60.92 (a, $O-CH_2-$), 166.94 (C=N); ms: [FAB(positive)] m/z 360.5(20), 151(9.0), 209(100); ir(nujol/ cm^{-1}) br. –NH 3274, C=N 1653, C-S 1338.

Anal. Calcd. for $C_{15}H_{28}N_4O_2S_2$: C, 50.0; H, 7.8; N, 15.5. Found: C, 49.8; H, 7.7; N, 15.4.

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