Synthesis and Temperature-Dependent Conformational Preferences of Macrocycles Containing the 2,2′-Bipyridyl Moiety

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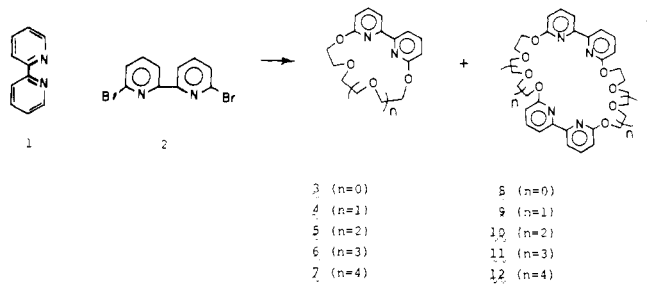
Abstract: The synthesis of 1:1 crown ether macrocycles containing a 2,2-bipyridyl subunit by nucleophilic displacement reactions by the dianion of oligomeric glycols is described. The NMR spectral data of these macrocycles indicate that the preferred conformations are ascertained by the size of the polyethereal bridge. Variable-temperature NMR studies of the penta- and hexaethylene glycol–bipyridyl macrocycles support a conformational rotation at diminished temperatures, in which the syn conformation is preferred at > -70 °C, whereas at room temperature the anti conformation is dominant. Detailed mathematical analysis suggests that only about 5% of molecule **6** occupies the anti conformation at -100 °C. However, the crystal structure determination of **6** was conducted, thus establishing its anti conformation in the solid state.

Numerous chelating reagents have been designed and created for analysis of metal ions, but few have received more attention than those of the 2,2′-bipyridyl class (**1**). Blau's initial discovery[3] of Fe(II) and Fe(III) complexation by this ligand at the turn of this century has sparked the ingenuity of chemists to devise more selective ligands, which have been based on the metamorphosis of the Schiff-base moiety of these bipyridyls. In 1972, a second-generation bipyridyl ligand was designed in which the bipyridyl moiety was used as a subunit within a macrocyclic framework.[4] Ogawa et al.[5] reported the inclusion of the 1,10-phenanthroline subunit into a macropolyheterocyclic framework, whereas later Buhleier and Vögtle[6] demonstrated the incorporation of either this same subunit or the bipyridyl moiety into a macrocycle via direct nucleophilic displacement of heteroaryl halides[7] with alkoxides or mercaptides. Bridged Schiff-base macrocycles[8,9] have also recently been synthesized from either 6,6′-dihydrazino-2,2′-bipyridyl or 2,9-di(methylhydrazino)-1,10-phenanthroline, macrocyclic bisamides[10] from 2,2′-bipyridyl-6,6′-dicarboxylic acid chloride with diverse diamines, and macrocyclic bisesters[11] from 2,2′-bipyridyl-3,3′-dicarboxylic acid.[11] Recently in our laboratories, the ring contraction of phosphorus macrocycles[12] and a ring-contractive decarbonylation of dipyridyl ketones[13] afforded unexpected new routes to crown-ether macrocycles possessing the 2,2′-bipyridyl unit. We herein report our original more traditional approach to these bipyridyl macrocycles as well as their temperature-dependent conformational preferences and configuration within the crystal. These studies suggest that different modes of ion complexation of conformationally mobile ligands may be possible depending upon the rotamer distribution at diminished temperatures.

Results

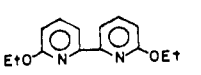
The starting material, 6,6′-dibromo-2,2′-bipyridyl (**2**),[14] was generated in ca. 60% yield from the copper-induced dimerization of 6-lithio-2-bromopyridine at -100 °C. Numerous alternate procedures have been utilized: (a) bis(6-bromo-2-pyridyl)mercury[15] with $K_2Ni_2(CN)_6$ in the presence of carbon monoxide[16] or in anhydrous *N,N*-dimethylformamide under ultraviolet light[17] and (b) direct halogenation of 2,2′-bipyridyl.[18] These procedures afforded variable 4–29% yields of **2** and thus no obvious advantage over the above coupling procedure. Decarbonylation of di(6-bromo-2-pyridyl) ketone[13] and dephosphorylation of di(6-bromo-2-pyridyl)phenylphosphine oxide[12] gave respectable yields (40–55%) of **2** but still offered no dramatic advantage.



Treatment of 2,6-dihalopyridine[7,19] and related heterocycles[20] with the dianion of polyethylene glycolate has been demonstrated to give macrocycles as well as numerous noncyclic compounds. When **2** was reacted with disodioethylene glycolate, prepared from the glycol and 2 equiv of sodium hydride in refluxing anhydrous xylene, the 1:1 macrocycle **4** was isolated in 2% yield along with recovered starting material. In this case, the formation of the larger 1:1 oligomer **4**, rather than **3**, was anticipated since (1) thermal oligomerization of polyethylene glycols has been previously demonstrated under these reaction conditions[7,19–21] and (2) a diethylene glycol bridge would be disfavored based on bridging distances[22] and bond deformation. The 2:2 macrocycle **8** was isolated in 7% yield, as well as the open-chain products; further characterization of the latter was not conducted.

The triethylene glycol bridged macrocycle **4** was prepared (9%) in a similar manner when **2** was treated with triethylene glycolate; the anticipated dimer **9** was also isolated (13%). The remaining tetra-, penta-, and hexaethylene glycolates with **2** gave **5, 6,** and **7** in 24, 28, and 30% yields, respectively, as well as the corresponding 2:2 macrocycles (**10, 11, 12**) in 15–20% yield.

Selected NMR spectral data for **4–7** and 6,6′-diethoxy-2,2′-bipyridyl (**13**) have been tabulated in Table I. In general,



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very little change in chemical shifts for the 4,5-pyridyl and α-methylene hydrogens is observed, whereas a significant shift is noted for the 3-pyridyl hydrogen with deviation of ethereal bridge size. With diminished ring size as in **4** and **5** only a syn conformation **14** is possible as indicated by the chemical-shift values, especially δ_{H3} ca 7.3, molecular models, and theoretical calculations.[22] However, with increased ring size inherent in **6** and **7**, the anti conformation **15** becomes accessible, as sug-

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Table I. Selected NMR Data for 1:1 Bipyridyl Macrocycles

compd	ring size	δ, ppm[a] 3	4	5	α-CH_2
4	16	7.31	7.63	6.73	4.70
5	19	7.39	7.58	6.73	4.71
6	22	7.74	7.63	6.75	4.81
7	25	7.86	7.67	6.77	4.73
13		7.93	7.54	6.71	4.51

[a] Spectral data obtained in $CDCl_3$ with Me_4Si as standard. [b] Reference 12.

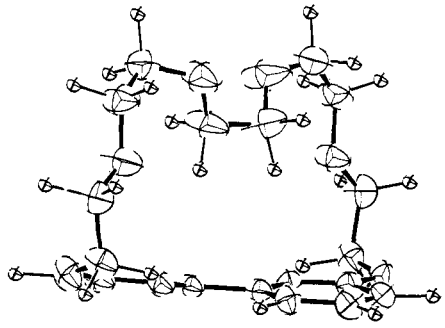


Figure 1. Perspective drawing (ORTEP) of macrocycle **6**, illustrating the conformation of the polyethereal chain.

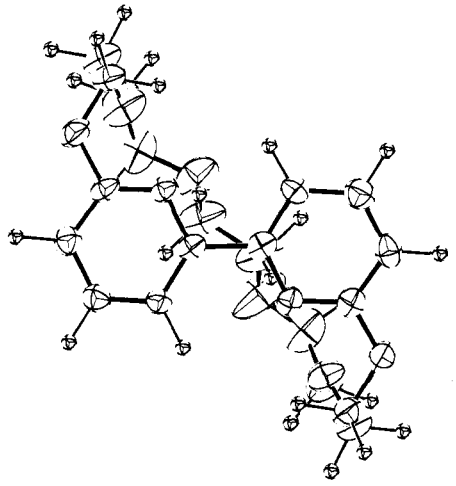
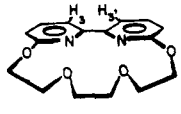


Figure 2. Perspective drawing (ORTEP) of macrocycle **6**, viewed normal to the plane of the bipyridyl group.

gested by the dramatic downfield shift ($\Delta\delta$ = 0.4–0.6 ppm) shown for the 3-pyridyl ring hydrogen. This shift reflects the increased diamagnetic anisotropy experienced by the 3-pyridyl hydrogens caused by the juxtaposition of the orthogonal N



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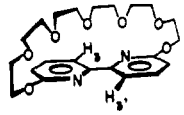

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electrons of the adjacent pyridine ring.[23] The maximum anisotropic shift for H-3 is realized by the open-chained model **13**,[12] in which no bridge constraints are imposed on the bipyridyl moiety and the anti conformation is favored as based on the correlation with dipole moment,[24,25] NMR,[23] and UV[23a,d,26] studies for the parent 2,2'-bipyridyl. In the crystalline state of **1**, the X-ray data further support the anti conformation (180° torsion angle).[27]

Table II. Macrocycle **6** Coordinates (×10^4) for Nonhydrogen Atoms

atom	X	Y	Z
N(1)	4692 (6)	8664 (3)	7488 (3)
N(2)	6499 (6)	9934 (3)	6041 (3)
O(1)	8107 (5)	10 620 (3)	5247 (2)
O(2)	8522 (7)	11 870 (3)	6581 (3)
O(3)	8632(7)	11 708 (3)	8346 (3)
O(4)	8137 (8)	10 267 (5)	9464 (3)
O(5)	6142 (6)	8674 (3)	9502 (3)
O(6)	3285 (5)	8116 (3)	8450 (3)
C(1)	3470 (9)	8727 (4)	7845 (4)
C(2)	2263 (8)	9376 (5)	7611 (4)
C(3)	2392 (9)	10 012 (5)	6999 (5)
C(4)	3683 (8)	9982 (4)	6626 (4)
C(5)	4804 (7)	9300 (4)	6894 (3)
C(6)	6255 (8)	9209 (4)	6536 (3)
C(7)	7259 (8)	8459 (4)	6710 (4)
C(8)	8577 (8)	8442 (4)	6355 (4)
C(9)	8840 (8)	9165 (5)	5850 (4)
C(10)	7766 (8)	9897 (4)	5728 (3)
C(11)	7230 (9)	11 481 (4)	5223 (4)
C(12)	8185 (10)	12 206 (5)	5758 (4)
C(13)	9377 (10)	12 464 (5)	7150 (4)
C(14)	9824 (9)	12 038 (6)	7966 (5)
C(15)	8110 (11)	10 821 (5)	8133 (5)
C(16)	7222 (10)	10 414 (5)	8705 (5)
C(17)	7658 (12)	9966 (7)	10 105 (5)
C(18)	7081 (10)	9042 (6)	10 210 (4)
C(19)	5407 (9)	7813 (4)	9617 (4)
C(20)	4545 (9)	7482 (4)	8782 (4)

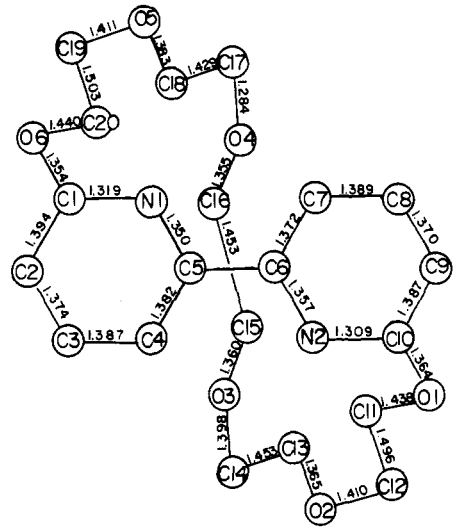

Figure 3. Bond distances for **6**. Standard deviations in these values are estimated to be 0.006–0.011 Å.

In order to verify the relationship between the parent bipyridyl and these larger macrocyclic systems, the crystal structure determination of **6** was undertaken. Table II lists the coordinates of the nonhydrogen atoms for **6**. Pertinent X-ray results are summarized in Figures 1–4, which illustrate prospective views of **6** as well as show the bond distances and angles between bonds. Anisotropic thermal and hydrogen atom parameters are included in the supplementary material. Macrocycle **6** is seen (Figure 2) to exist in the crystal in essentially the anti conformation, with the torsion angle about the central bond of the bipyridyl group of 171°. This value is comparable to that of exactly 180° for bipyridyl, in which the molecule was demonstrated to be *planar* and *trans*.[27b]

Although the molecule occupies an asymmetric position in the crystal structure, macrocycle **6** approximates C_2 symmetry

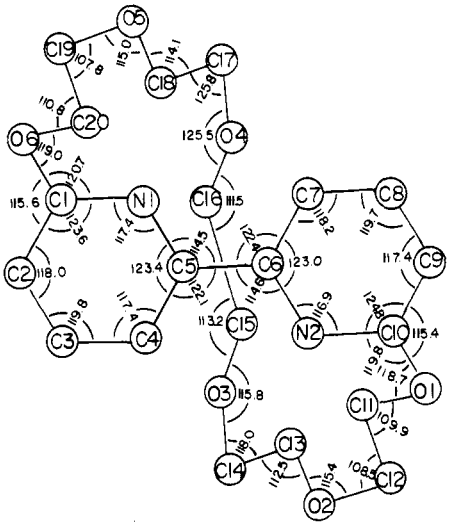

Figure 4. Bond angles for **6**. Standard deviations in these values are estimated to be 0.5–0.7°.

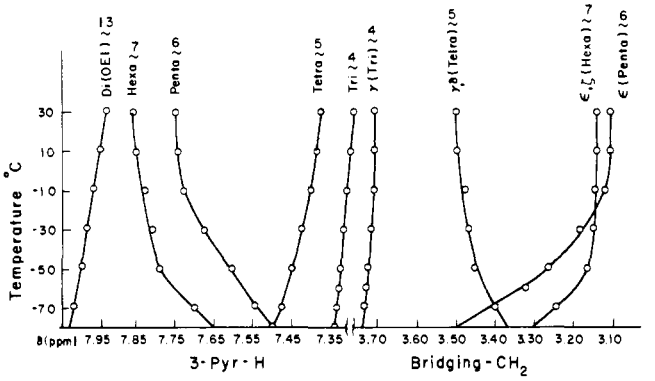

Figure 5. VT NMR data for the 3-pyr-H and central bridging methylene group(s) in **4**–**7**.

reasonably well, as is obvious from Figure 1. The distances and angles of the two heteroaromatic rings are identical within experimental error around the approximate twofold axis and only in parts of the polyethereal bridge do statistically significant differences appear. All distances and angles are chemically reasonable; those near the center of the polyethereal chain are affected to some degree by the large thermal motion, which this portion of the molecule undergoes in the crystal. Distances within the bipyridyl fragment exhibit some statistically significant variations from those of 2,2′-bipyridyl; however, those are attributed to possible electronic effects of the ethereal substitution and the imidate ester characteristics [-N=C-OCH_2-] within these macrocycles.[28] The linkage of the polyethereal chain to the pyridine ring is approximately in the plane of the ring and cis to the nitrogen; conformational rigidity suggested by this low dihedral angle appears to restrict flexibility with these macrocycles.[19b,20c,29]

While **6** and **7** can occupy the anti conformation at room temperature, variable-temperature NMR studies show a distinct syn conformational preference for the bipyridyl moiety at low temperatures. Population of the syn conformation increases as the temperature is lowered below ca. −10 °C. Data presented in Figure 5 suggest that the anti conformation is no longer accessible when the temperature falls somewhat below −70 °C. The syn orientation at low temperatures is indicated by (1) decreased anisotropic effect at the 3-pyridyl hydrogen due to the N electrons of the adjacent pyridine ring, resulting in a similar aromatic NMR pattern to that of the syn macrocycle **4**, and (2) a significantly diminished ring anisotropy inflicted on the central (ϵ and/or ξ) bridging methylenes. This latter phenomenon has also been demonstrated in **16**,[30] in which the bridge must be subjected to the direct environment of the naphthyridine π face. Separation of the oxygen atoms bonded to the bipyridyl group decreases from 8.42 to 6.94 Å when the conformation changes from anti to syn. Since the mean square unperturbed end-to-end distance of polyoxyethylene is known to *decrease* upon cooling,[31] it is to be expected that a reduction in temperature will increase the population of the syn conformation. Detailed theoretical analysis[22] of the behavior of the polyoxyethylene moiety in **6** provides support for this contention. It predicts a decline in population of the anti conformation as the temperature decreases below 0 °C. At −100 °C, only about 5% of the molecules would occupy the anti conformation. Data in Figure 5 show that bipyridyls **5** and **13** show little deviation from the syn and anti equilibrium conformations, respectively, upon lowering the temperatures. Thus, a conformational preference, experienced by the bipyridyl unit, is instilled into these larger macrocycles by a contractive orientation imposed predominantly by the polyoxyethylene bridge. Okahara et al. recently demonstrated a similar temperature dependence in the templated synthesis of simple crown ethers.[32]

Preliminary complexation studies of **6** by NMR indicate that upon addition of sodium iodide the syn conformer, in which the sodium ion is associated with the ethereal portion of the macrocycle and not necessarily within the cavity, is preferred. Europium shift studies on **6** further suggest predominant external complexation with the central ethereal bridging oxygens, as evidenced by the dramatic shift of the ϵ protons and a distinct preference toward the anti conformer at less than 20% added shift reagent.[33] Studies on these macrocycles to elucidate the nature of this conformational preference and subsequent ramifications on complexation are in progress.

Experimental Section

General Comments. All melting points were taken in capillary tubes with a Thomas-Hoover Uni-Melt and are uncorrected. Infrared (IR) and ultraviolet (UV) spectra were recorded on Beckman IR-7 and Cary 14 spectrophotometers, respectively. Unless otherwise noted, ^{1}H NMR spectra were determined in deuteriochloroform (10% w/v) solutions with Me_4Si as internal standard (δ 0 ppm) and recorded on either a Varian Associates A-60A or HA-100 spectrometer. Molecular weights were determined with either a Hewlett-Packard 302 vapor pressure osmometer or a Hitachi Perkin-Elmer RMS-4 mass spectrometer by Mr. J. Murphy.

The recorded R_f values were determined by a standardized thin layer chromatography (TLC) procedure: 0.25-mm Brinkmann silica gel 60 HF-254+366 plates eluting with cyclohexane–ethyl acetate (1:2). For preparative chromatography (ThLC), 2-mm Brinkmann silica gel PF-254+366 plates were used, eluting with stipulated solvent(s). Elemental analyses were performed by Mr. R. Seab in these laboratories.

All reaction solvents were distilled from sodium under nitrogen. Sodium hydride (57% oil dispersion) was initially washed with anhydrous petroleum ether (bp 30–60 °C), then dried in vacuo prior to the reaction. Di-, tri-, and tetraethylene glycols were purchased from Aldrich Chemical Co., whereas penta- and hexaethylene glycols were purchased from Columbia Organic Chemicals. All glycol reagents were distilled in vacuo prior to use.

X-ray Experimental. Prismatic, colorless crystals of the 1:1 bipyridyl–pentaethylene glycol macrocycle (**6**), grown from a cyclohexane solution by slow evaporation, proved to be of sufficient quality for the X-ray diffraction studies. Crystals grown from either ethyl acetate or ethanol–diethyl ether solutions were similar in appearance but diffracted X-rays diffusely, thus could not be used. A fairly equant crystal of dimensions ca. 0.60 mm was sealed in a thin-walled glass capillary and mounted in a random orientation on an Enraf-Nonius CAD-4 diffractometer. All measurements were made using graphite monochromatized Mo Kα radiation at ambient temperature of 24 ±

2 °C. Unit cell dimensions and crystal orientation were determined from the diffractometer coordinates of 15 accurately centered reflections having $10° > \theta > 6°$.

Crystal Data. $C_{20}H_{26}N_2O_6$ had mol wt 390.4; monoclinic space group $P2_1/a$; $a = 8.712$ (3) Å, $b = 14.205$ (5) Å, $c = 16.458$ (5) Å, $\beta = 101.60$ (2)°, $V = 1995$ Å^3, $Z = 4$, $d_c = 1.30$ g cm^{-3}, $\lambda = 0.710\,69$ Å, μ(Mo $K\alpha$) = 0.901 cm^{-1}.

Intensity data were collected by the ω–2θ scan technique employing variable scan rates. The scan rate to be used for each measurement was determined by performing a fast (20 deg min^{-1}) prescan. If the prescan net intensity totaled greater than 2000 counts, it was accepted as the final scan. If the prescan intensity totaled fewer than 30 net counts, the reflection was tagged as unobserved, and no slow scan was made. For intermediate values, the scan speed was adjusted to yield a net intensity of 2000 counts. The maximum time spent on any slow scan was set at 180 s.

Scan widths varied with θ to allow for α_1–α_2 splitting; the scan width function was $(0.80 + 0.20 \tan \theta)°$. The calculated scan angle was increased by 25% at each extreme, with these extents serving as background measurements. During data collection, two standard reflections were remeasured every 75 measurements; these exhibited no significant decline in intensity. All data in one quadrant having $1° \leq \theta \leq 20°$ were measured at least once by the above procedure.

Of the 2131 reflections measured, 1319 were treated as "observed" by the diffractometer and were used in further computations. Background, Lorentz, and polarization corrections were made to the data, but no absorption corrections were deemed necessary owing to the very low linear absorption coefficient.

Structure Solution and Refinement. The space group is uniquely determined by systematic absence $0k0$ with k odd and $h0l$ with h odd. The structure was solved by routine application of the multiple-solution direct phasing method,[34] using program MULTAN 74. Of the 28 nonhydrogen atoms of the structure, 26 were located from the highest overall figure-of-merit E map, and the remaining two atoms were located by a difference Fourier synthesis. Machine calculations were conducted on an IBM 3033 computer using primarily the XRAY 72[35] system of programs. The model was refined by least-squares techniques employing unit weights. The function minimized was $\sum(|F_o| - |F_c|)^2$, and the refined variables were divided into three blocks. Nonhydrogen atoms were treated anisotropically, while hydrogen atoms were fixed in calculated positions, 1 Å distant from the carbon atoms to which they are bonded, with isotopic thermal parameters estimated based upon thermal parameters of the carbon atoms. Neutral atom scattering factors for C, N, and O were taken from the compilation of Cromer and Mann;[36] H atom scattering factors were those of Stewart, Davidson, and Simpson.[37] One reflection (220) was banned on the basis of grossly unequal backgrounds, and thus not used in the refinement. Refinement converged with $R_1 = \sum(|F_o| - |F_c|)/\sum|F_o| = 0.059$ and $R_2 = \{\sum(|F_o| - |F_c|)^2/\sum|F_o|^2\}^{1/2} = 0.53$. A difference Fourier synthesis calculated at the conclusion of the refinement exhibited no feature greater than ±0.22 e Å^{-3}. Refined coordinates are given in Table II, and refined thermal parameters as well as assigned hydrogen atom parameters are given in the supplementary material.

6,6'-Dibromo-2,2'-bipyridyl (2). A solution of 2-bromo-6-lithiopyridine [prepared from 2,6-dibromopyridine (10.0 g, 0.042 mol) and *n*-butyllithium (2.23 M in hexane, 18.8 mL, 0.042 mol)] in diethyl ether (150 mL) was cooled via a liquid nitrogen–petroleum ether bath to −100 °C and powdered cupric chloride (2.18 g, 0.22 mol) was added slowly. The mixture was allowed to warm to −70 °C with *efficient stirring.* [Caution: Reaction may become exothermic at this point!] After 1 h, oxygen was slowly bubbled through the solution until a pale green coloration occurred (ca. 30 min). Then aqueous HCl (5 N, 100 mL) was added carefully to quench the reaction. After filtration, the ether was removed affording a residue which was extracted several times with benzene. The combined benzene extracts after concentration afforded 3.7 g (56.2%) of white, crystalline material corresponding to 6,6'-dibromo-2,2'-bipyridyl, mp 219–220 °C (from chloroform, lit.[14] mp 218 °C).

Reaction of 6,6'-Dibromo-2,2'-bipyridyl with Diethylene Glycol, General Procedure. To a suspension of oil-free sodium hydride (240 mg, 10 mmol) in anhydrous xylene (150 mL), diethylene glycol (530 mg, 5 mmol) was added slowly with stirring under nitrogen. After 15 min, **2** (1.57 g, 5 mmol) was added via a solid addition funnel. The mixture was refluxed for 24 h, then cooled and quenched with careful addition of water. The aqueous layer was separated and extracted several times with methylene chloride. The combined organic layers were dried over anhydrous magnesium sulfate and concentrated in vacuo to afford an oily residue, which was chromatographed (ThLC) eluting two times with cyclohexane–ethyl acetate (1:1) to give the following components.

Fraction A gave unreacted starting material **2**, 400 mg (26%), mp 222–224 °C.

Fraction B gave a white residue, which after recrystallization from 95% ethanol gave colorless crystals corresponding to macrocycle **4**: mp 106–108 °C; 45 mg (2%); R_f 0.42; NMR δ 3.77 (s, γ-CH_2O, 4 H), 4.01 (t, β-CH_2O, J = 5 Hz, 4 H), 4.70 (t, α-CH_2O, J = 5 Hz, 4 H), 6.73 (dd, 5,5'-pyr-H, J = 8, 1 Hz, 2 H), 7.31 (dd, 3,3'-pyr-H, J = 7.5, 1 Hz, 2 H), 7.63 (dd, 4,4'-pyr-H, J = 8, 7.5 Hz, 2 H); IR (KBr) 2950, 1585, 1445, 1310, 1150, 1075, 980, 750 cm^{-1}; UV (ethanol) λ_{max} (ϵ) 236 (0.13 × 10^5), 305 (0.65 × 10^4), 310 nm (0.79 × 10^4).

Anal. Calcd for $C_{16}H_{18}N_2O_4$: C, 63.57; H, 5.96; N, 9.27; mol wt, 302. Found: C, 63.32; H, 6.13; N, 9.10; mol wt (osmometry), 306 (av).

Fraction C, after recrystallization from 95% ethanol, gave the 2:2 macrocycle **8**: mp 103–105 °C; 85 mg (7%); R_f 0.39; NMR δ 3.95 (t, β-CH_2O, J = 5 Hz, 8 H), 4.58 (t, α-CH_2O, J = 5 Hz, 8 H), 6.78 (dd, 5,5'-pyr-H, J = 7.5, 1.5 Hz, 4 H), 7.50 (dd, 3,3'-pyr-H, J = 8, 1.5 Hz, 4 H), 7.65 (dd, 4,4'-pyr-H, J = 8, 7.5 Hz, 4 H); IR (KBr) 2970, 1610, 1590, 1445, 1275, 1130, 990, 800 cm^{-1}.

Anal. Calcd for $C_{28}H_{28}N_4O_6$: C, 65.11; H, 5.45; N, 10.85; mol wt, 516. Found: C, 65.06; H, 5.51; N, 10.76; mol wt (osmometry), 523 (av).

Reaction of 6,6'-Dibromo-2,2'-bipyridyl with Triethylene Glycol. The general procedure was followed except for the substitution of triethylene glycol (750 mg, 5 mmol). After standard workup, the residue was chromatographed (ThLC) eluting two times with cyclohexane–ethyl acetate (1:1) affording the following fractions.

Fraction A gave 156 mg (10%) of starting material, mp 222–224 °C.

Fraction B gave an oily material (7 mg), which was not characterized.

Fraction C, after recrystallization from ethanol, gave shining needles of macrocycle **4**, mp 106–108 °C, 135 mg (9%).

Fraction D was recrystallized from ethanol as colorless plates corresponding to the 2:2 macrocycle **9**: mp 146–148 °C; 200 mg (13%); R_f 0.31; NMR δ 3.71 (s, γ-CH_2O, 8 H), 3.83 (t, β-CH_2O, J = 5 Hz, 8 H), 4.45 (t, α-CH_2O, J = 5 Hz, 8 H), 6.53 (dd, 5,5'-pyr-H, J = 7.5, 1 Hz, 4 H), 7.71 (dd, 3,3'-pyr-H, J = 8, 1 Hz, 4 H), 7.40 (dd, 4,4'-pyr-H, J = 8, 7.5 Hz, 4 H); IR (KBr) 2950, 1590, 1315, 1075, 990, 850, 750 cm^{-1}.

Anal. Calcd for $C_{32}H_{36}N_4O_8$: C, 63.57; H, 5.96; N, 9.27; mol wt, 604. Found: C, 63.42; H, 5.84; N, 9.19; mol wt (osmometry), 614 (av).

Reaction of 6,6'-Dibromo-2,2'-bipyridyl with Tetraethylene Glycol. The general procedure was followed except for the substitution of tetraethylene glycol (970 mg, 5 mmol). The various components were separated by ThLC eluting four times with cyclohexane–ethyl acetate (1:1). The following major fractions were separated and characterized.

Fraction A gave unreacted **2**, 50 mg (3%), mp 221–223 °C.

Fraction B, after recrystallization from ethanol, gave 1:1 macrocycle **4** as colorless plates, mp 106–108 °C, 30 mg (1%).

Fraction C was recrystallized from 95% ethanol to afford the 1:1 macrocycle **5**, as colorless needles: mp 99–101 °C; 400 mg (24%); R_f 0.20; NMR δ 3.47 (m, δ-CH_2O, 4 H), 3.65 (m, γ-CH_2O, 4 H), 3.93 (t, β-CH_2O, J = 5 Hz, 4 H), 4.71 (t, α-CH_2O, J = 5 Hz, 4 H), 6.73 (dd, 5,5'-pyr-H, J = 8, 1 Hz, 2 H), 7.34 (dd, 3,3'-pyr-H, J = 8, 1 Hz, 2 H), 7.58 (t, 4,4'-pyr-H, J = 8 Hz, 2 H); IR (KBr) 2900, 2850, 1590, 1432, 1250, 1050, 930, 750 cm^{-1}; UV (ethanol) λ_{max} (ϵ) 230 (2.6 × 10^4), 310 (3.1 × 10^4), 317 nm (1.8 × 10^4).

Anal. Calcd for $C_{18}H_{22}N_2O_5$: C, 62.42; H, 6.35; N, 8.09; mol wt, 346. Found: C, 62.32; H, 6.17; N, 8.06; mol wt (MS), *m/e* 346 (M^+).

Fraction D was obtained, in insufficient quantity and quality, as an oil (17 mg, R_f 0.17). Further identification was not conducted.

Fraction E was isolated as a viscous liquid, which solidified upon standing. After recrystallization from ethanol, the 2:2 macrocycle **10** was obtained as colorless needles: mp 121–122 °C; 260 mg (15%); R_f 0.15; NMR δ 3.71 (bs, γ-, δ-CH_2O, 16 H), 3.92 (t, β-CH_2O, J = 5 Hz, 8 H), 4.51 (t, α-CH_2O, J = 5 Hz, 8 H), 6.61 (dd, 5,5'-pyr-H, J = 8, 1 Hz, 4 H), 7.46 (t, 4,4'-pyr-H, J = 8 Hz, 4 H), 7.70 (dd, 3,3'-

pyr-H, 4 H); IR (KBr) 2910, 1582, 1460, 1303, 1136, 1052, 950, 790 cm^{-1}.

Anal. Calcd for $C_{36}H_{44}N_4O_{10}$: C, 62.42; H, 6.35; N, 8.09; mol wt, 692. Found: C, 62.43; H, 6.38; N, 8.05; mol wt (MS), *m/e* 692 (M^+).

Reaction of 6,6'-Dibromo-2,2'-bipyridyl with Pentaethylene Glycol. The general procedure was followed except for the substitution of pentaethylene glycol (1.19 g, 5 mmol). After workup, the brown, viscous oil was chromatographed (ThLC) eluting four times with cyclohexane–ethyl acetate (1:2) affording the following fractions.

Fraction A gave starting material, 58 mg (4%), mp 221–223 °C.

Fraction B, after recrystallization from ethanol, gave **5**, mp 99–101 °C, 40 mg (2%),

Fraction C was purified by sublimation in vacuo [80 °C (1 mm)] to give 1:1 macrocycle **6** as colorless needles: mp 90–92 °C; 506 mg (28%); R_f 0.13; NMR δ 3.15 (s, ξ-CH_2O, 4 H), 3.36 (t, δ-CH_2O, J = 5 Hz, 4 H), 3.58 (t, γ-CH_2O, J = 5 Hz, 4 H), 3.93 (t, β-CH_2O, J = 5 Hz, 4 H), 4.81 (t, α-CH_2O, J = 5 Hz, 4 H), 6.75 (dd, 5,5'-pyr-H, J = 8, 1 Hz, 2 H), 7.63 (t, 4,4'-pyr-H, J = 8 Hz, 2 H), 7.74 (dd, 3,3'-pyr-H, J = 8, 1 Hz, 2 H); IR (KBr) 2930, 1590, 1456, 1324, 1276, 1100, 950, 750 cm^{-1}; UV (ethanol) λ_{max} (ϵ) 220 (3.7×10^4), 307 (0.8×10^4), 315 nm (2.0×10^4).

Anal. Calcd for $C_{20}H_{26}N_2O_6$: C, 61.53; H, 6.66; N, 7.17; mol wt, 390. Found: C, 51.34; H, 6.79; N, 7.04; mol wt (MS), *m/e* 390 (M^+).

Fraction D, after recrystallization from ethanol, afforded 2:2 macrocycle **11** as colorless plates: mp 99–101 °C; 320 mg (16%); R_f 0.08; NMR δ 3.65 (bd, γ-, ω-CH_2O, 24 H), 3.88 (t, β-CH_2O, J = 5 Hz, 8 H), 4.55 (t, α-CH_2O, J = 5 Hz, 8 H), 6.71 (dd, 5,5'-pyr-H, J = 8, 1 Hz, 4 H), 7.58 (t, 4,4'-pyr-H, J = 8 Hz, 4 H), 7.88 (dd, 3,3'-pyr-H, J = 8, 1 Hz, 4 H); IR (KBr) 2950, 1580, 1310, 1135, 950, 750 cm^{-1}.

Anal. Calcd for $C_{40}H_{52}N_4O_{12}$: C, 61.53; H, 6.66; N, 7.17; mol wt, 780. Found: C, 61.59; H, 6.89; N, 7.05; mol wt (MS), *m/e* 780 (M^+).

Reaction of 6,6'-Dibromo-2,2'-bipyridyl with Hexaethylene Glycol. The general procedure was followed except for the substitution of hexaethylene glycol (1.41 g, 5 mmol). After workup the residue was chromatographed (ThLC) eluting four times with cyclohexane–ethyl acetate (1:2) to give the following fractions.

Fraction A gave 10 mg (1%) of unreacted starting material, mp 221–223 °C.

Fraction B was recrystallized from ethanol to afford 1:1 macrocycle **6** as colorless plates, mp 90–92 °C, 52 mg (2%).

Fraction C was sublimed in vacuo [80 °C (1 mm)] to give colorless, crystalline needles of macrocycle **7**: mp 41–43 °C; 670 mg (30%); R_f 0.10; NMR δ 3.17 (m, ξ-CH_2O, 4 H), 3.28 (m, ϵ-CH_2O, 4 H), 3.45 (m, δ-CH_2O, 4 H), 3.68 (m, γ-CH_2O, 4 H), 3.94 (t, β-CH_2O, J = 5 Hz, 4 H), 4.73 (t, α-CH_2O, J = 5 Hz, 4 H), 6.77 (dd, 5,5'-pyr-H, J = 8, 1 Hz, 2 H), 7.67 (dd, 4,4'-pyr-H, J = 8, 8 Hz, 2 H), 7.90 (dd, 3,3'-pyr-H, J = 8, 1 Hz, 2 H); IR (KBr) 2870, 1476, 1455, 1325, 1125, 1110, 940, 800, 750 cm^{-1}; UV (ethanol) λ_{max} (ϵ) 236 (2.6×10^4), 301 (1.6×10^4), 310 nm (1.8×10^4).

Anal. Calcd for $C_{22}H_{30}N_2O_7$: C, 60.82; H, 6.91; N, 6.45; mol wt, 434. Found: C, 60.85; H, 6.96; 6.40; mol wt (MS), *m/e* 434 (M^+).

Fraction D gave 43 mg (2%) of crystalline macrocycle **11**, mp 99–101 °C.

Fraction E after recrystallization from ethanol afforded silky, crystalline needles corresponding to 2:2 macrocycle **12**: mp 70–72 °C; 350 mg (20%); R_f 0.05; NMR δ 3.43 (bd, γ-ξ-CH_2O, 32 H), 3.65 (t, β-CH_2O, J = 5 Hz, 8 H), 4.54 (t, α-CH_2O, J = 5 Hz, 8 H), 6.73 (dd, 5,5'-pyr-H, J = 8, 1 Hz, 4 H), 7.63 (t, 4,4'-pyr-H, J = 8 Hz, 4 H), 7.91 (dd, 3,3'-pyr-H, J = 8, 1 Hz, 4 H); IR (KBr) 2950, 1585, 1305, 1270, 1135, 1100, 942, 750 cm^{-1}.

Anal. Calcd for $C_{44}H_{60}N_4O_{14}$: C, 60.82; H, 6.91; N, 6.45; mol wt, 868. Found: C, 60.75; H, 7.02; N, 6.39; mol wt (MS), *m/e* 868 (M^+).

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Supplementary Material Available: Coordinates and isotropic thermal parameters for H atoms of macrocycle **6** (Table III), anisotropic thermal parameters (Table IV), and the observed and calculated structure factors for macrocycle **6** (Table V) (13 pages). Ordering information is given on any current masthead page.

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Molecular Origin of the Temperature-Dependent NMR Spectrum of 1:1 Crown Ether Macrocycles Containing a 2,2′-Bipyridyl Subunit

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Abstract: A strongly temperature-dependent NMR spectrum has been reported for certain cyclic molecules prepared from 2,2′-bipyridyl and polyoxyethylene oligomers (x-mers). A study of the conformational characteristics of this class of cyclic molecules was undertaken to attempt an identification of the molecular origin of the temperature-dependent NMR. The polyoxyethylene chain in an acyclic analogue is assumed to behave according to the rotational isomeric state model developed by Mark and Flory for unperturbed polyoxyethylene. Monte Carlo calculations were performed using a priori and conditional probabilities deduced from the rotational isomeric state model. Calculations predict that cyclization is impossible for $x = 2$, barely possible for $x = 3$, and most readily achieved with $x = 5$–7, in reasonable accord with experiment. Many polyoxyethylene chain conformations are consistent with cyclization when $x = 6$. Cyclization is achieved with little change in probabilities for occupancy of trans and gauche states by bonds in the polyoxyethylene chain of this molecule. Calculations were repeated using a priori and conditional probabilities appropriate for temperatures of −125 to 125 °C. The polyoxyethylene chain conformation at low temperature can most easily achieve cyclization if the rotational state about the bond between the aromatic rings tends toward cis. In these conformations the polyoxyethylene chain occupies a position away from the face of the aromatic system. As the temperature increases, cyclization also becomes possible if the rotational state about this bond tends toward trans. Part of the polyoxyethylene moiety is then drawn across the face of the aromatic system. The temperature-dependent NMR is a consequence of thermal alteration in the distribution of polyoxyethylene chain conformations consistent with cyclization.

A variety of configuration-dependent properties of large, flexible chain molecules are susceptible to rationalization via rotational isomeric state theory.[1,2] Branched molecules may also be treated with no sacrifice in rigor.[3] Macrocycles are profitably investigated via rotational isomeric state theory only if they are large enough to possess a relatively large number of strain-free configurations.[4] Molecules of the type shown in Figure 1a should fulfill this requirement if x exceeds about 4. This series of molecules is of particular interest because certain members, notably that with $x = 6$, exhibit marked changes in the NMR spectrum of their polyoxyethylene portion upon cooling.[5] These spectra suggest that the polyoxyethylene chain is less likely to be drawn across the face of the aromatic ring system at lower temperatures. We herein report that the probable molecular explanation for this observation is revealed by a rotational isomeric state treatment.

Calculations

Background. A cyclic molecule obtained from 2,2′-bipyridyl and an x-mer of polyoxyethylene is depicted in Figure 1a. For present purposes it will be convenient to imagine its synthesis from the open-chain analogue depicted in Figure 1b. Numerous conformations are available to the open-chain analogue. Conformation-dependent properties will be determined primarily by the polyoxyethylene portion, if x is large. Polyoxyethylene chain statistics have been studied in detail by Mark and Flory.[6,7] They developed a rotational isomeric state treatment which affords excellent agreement with the experimentally observed characteristic ratio and dipole moment, as well as the temperature dependence of these properties. Their treatment allows 21 conformations for each internal oxyethylene unit. If two states are also assigned to each pyridine–oxygen bond, the total number of conformations for the open-chain analogue is $4(21)^x$. When x is six, this model allows 343×10^6 conformations! Cyclization requires joining the free ends of the terminal virtual bonds (heavy lines in Figures 1a and 1b. Only a small subset of the $4(21)^x$ conformations of the open-chain analogue will be compatible with cyclization. The properties of this subset are the subject of this work.

The approach adopted has its origin in a recent theory of macrocyclization propounded by Flory and co-workers.[4] It is conveniently described with the aid of Figure 2, which schematically depicts the open-chain analogue in a configuration nearly compatible with cyclization. The first vector (from "atom" 0 to "atom" 1) denotes the virtual bond between the centers of the two pyridine rings in Figure 1a. This bond will be denoted by $\mathbf{l}_1$, and in general $\mathbf{l}_i$ is the vector from atom $i - 1$ to atom i. Virtual bond vector $\mathbf{l}_2$ extends from the center of the pyridine ring to the attached oxygen atom, while $\mathbf{l}_n$ extends from the attached oxygen atom on the other pyridine ring to the center of that ring. Thus "atom" 0 and "atom" n occupy the same position in the cyclic molecule. In the open-chain analogue $\mathbf{r}$ denotes the vector from "atom" 0 to "atom" n; the length of $\mathbf{r}$ is zero in the cyclic molecule.

An additional property of the cyclic molecule is that the angle between $\mathbf{l}_1$ and $\mathbf{l}_2$ is identical with the angle between $\mathbf{l}_1$ and $\mathbf{l}_n$. Adherence to this requirement is achieved through the device of creating a hypothetical bond between "atoms" n and $n + 1$ (Figure 2),[4] with $\theta_1 = \theta_n$. Bond angle requirements in the cyclic molecule are satisfied when the angle, $\Delta\theta$, between $\mathbf{l}_1$ and $\mathbf{l}_{n+1}$ is zero.

A final requirement in the cyclic molecule is that φ_1, the

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