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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 oxy-

ethylene 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 l_1, and in general l_i is the vector from atom $i - 1$ to atom i. Virtual bond vector l_2 extends from the center of the pyridine ring to the attached oxygen atom, while 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 l_1 and l_2 is identical with the angle between l_1 and 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 l_1 and l_{n+1} is zero.

A final requirement in the cyclic molecule is that φ_1, the
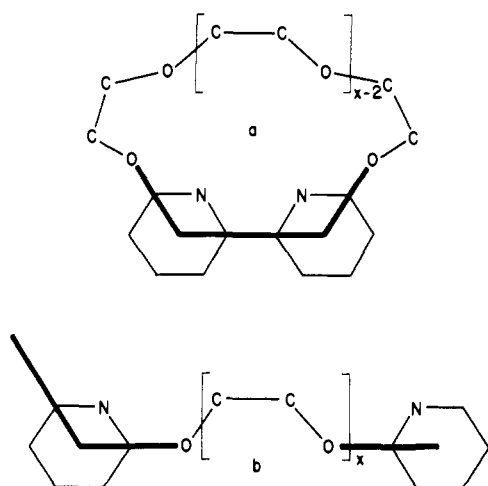
Figure 1. (a) Cyclic molecule prepared from 2,2'-bipyridyl and an *x*-mer of polyoxyethylene. Virtual bonds with one or two ends at the center of a pyridine ring are denoted by heavy lines. Hydrogen atoms are omitted. (b) Open-chain analogue of the molecule in (a). The virtual bonds are denoted by heavy lines.

Figure 2. Schematic open-chain analogue in a conformation nearly compatible with cyclization. See text for details.

dihedral angle describing rotation about virtual bond 1, must be allowed by the potential for rotation about the bond joining the aromatic rings. No a priori restrictions will be placed on φ_1. Instead one objective will be to ascertain which values are adopted by φ_1 as $r \rightarrow 0$ and $\Delta\theta \rightarrow 0$, given that the polyoxyethylene portion behaves in accord with the model developed by Mark and Flory.[6,7]

Geometry. The structure of 2,2'-bipyridyl in the crystalline state[8] yields $l_1 = 4.45$ Å and $\theta_1 = \theta_n = 62.4°$. Lengths of bonds in the polyoxyethylene chain are 1.43 and 1.53 Å for C–O and C–C, respectively, and supplements of the bond angles are 70°.[6] Lengths of virtual bonds 2 and n are 2.69 Å if the C_{ar}–O bond has the typical length of 1.36 Å.[9] Bond lengths and bond angles are held constant.

Statistical Weight Matrices. Statistical weight matrices used by Mark and Flory for the bonds in polyoxyethylene are reproduced in eq 1–3.[6,7]

$$U_{C-C} = \begin{bmatrix} 1 & \sigma' & \sigma' \\ 1 & \sigma' & \sigma'\omega \\ 1 & \sigma'\omega & \sigma' \end{bmatrix} \quad (1)$$

$$U_{C-O} = \begin{bmatrix} 1 & \sigma & \sigma \\ 1 & \sigma & \sigma\omega \\ 1 & \sigma\omega & \sigma \end{bmatrix} \quad (2)$$

$$U_{O-C} = \begin{bmatrix} 1 & \sigma & \sigma \\ 1 & \sigma & 0 \\ 1 & 0 & \sigma \end{bmatrix} \quad (3)$$

These statistical weight matrices are used for bonds 4 through $n - 2$ in the open-chain analogue. Columns index the state of the bond in question, while rows index the state of the preceding bond. In each case, the order of indexing is trans, gauche$^+$, gauche$^-$ (t, g$^+$, g$^-$), and dihedral angles for these three states are 180, 300, and 60°, respectively. Conformation-dependent properties of polyoxyethylene are reproduced using $E_\sigma = 900 (\pm 70)$ cal/mol, $E_{\sigma'} = -430 (\pm 70)$ cal/mol, and $E_\omega = 350 (\pm 200)$ cal/mol.[6,7]

Additional statistical weight matrices are required for bonds near the aromatic rings. Two equally weighted states (at $\pm$ 90°) are used for virtual bonds 2 and n. Three states (t, g$^\pm$) are
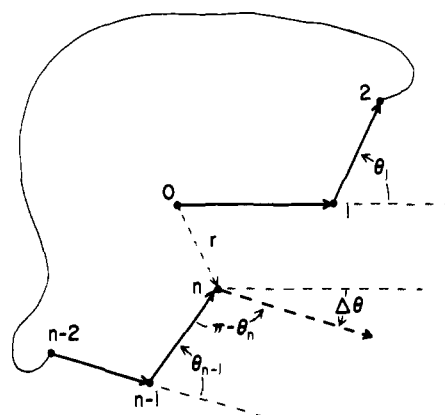
assigned to bonds 3 and $n - 1$. A repulsive first-order interaction between a methylene group and aromatic ring occurs in the g$^\pm$ states. The statistical weight is σ'' and $E_{\sigma''}$ is estimated to be 2000 cal/mol. On this basis, unity is used for U_1, $U_2 = $ row (1,1), $U_{n+1} = $ col (1,1), and U_3, U_{n-1}, and U_n are given by eq 4–6.

$$U_3 = \begin{bmatrix} 1 & \sigma'' & \sigma'' \\ 1 & \sigma'' & \sigma'' \end{bmatrix} \quad (4)$$

$$U_{n-1} = \begin{bmatrix} 1 & \sigma'' & \sigma'' \\ 1 & \sigma'' & \sigma''\omega \\ 1 & \sigma''\omega & \sigma'' \end{bmatrix} \quad (5)$$

$$U_n = \begin{bmatrix} 1 & 1 \\ 1 & 1 \\ 1 & 1 \end{bmatrix} \quad (6)$$

Generation of Representative Configurations. The number of conformations (343×10^6 for $x = 6$) for the open-chain analogue is too large to permit examination of each one in turn. Instead the objective is to examine a representative sample selected using Monte Carlo methods. Chains in representative conformations are grown using a priori and conditional probabilities calculated from the configuration partition function.[1,2] The configuration partition function, Z, is

$$Z = U_1^{(n+1)} \quad (7)$$

where $U_a^{(b)}$ denotes the serial product of b successive statistical weight matrices, commencing with U_a. The a priori probability that bond i is in state η is

$$p_{\eta;i} = Z^{-1} U_1^{(i-1)} U'_{\eta;i} U_{i+1}^{(n+1-i)} \quad (8)$$

while the a priori probability that bonds $i - 1$ and i simultaneously adopt states ξ and η is

$$p_{\xi\eta;i} = Z^{-1} U_1^{(i-1)} U'_{\xi\eta;i} U_{i+1}^{(n+1-i)} \quad (9)$$

The matrix $U'_{\eta;i}$ is obtained by zeroing out all columns of U_i except the column indexed by state η. Matrix $U'_{\xi\eta;i}$ is obtained from U_i by replacing all elements by zero except the one in row ξ, column η. The conditional probability that bond i is in state η, given that bond $i - 1$ is known to be the state ξ, is

$$q_{\xi\eta;i} = p_{\xi\eta;i}/p_{\xi;i-1} \quad (10)$$

Representative samples of chains were selected using $p_{\eta;2}$, $q_{\xi\eta;i}$ ($i = 3,n$), and a random number generator.
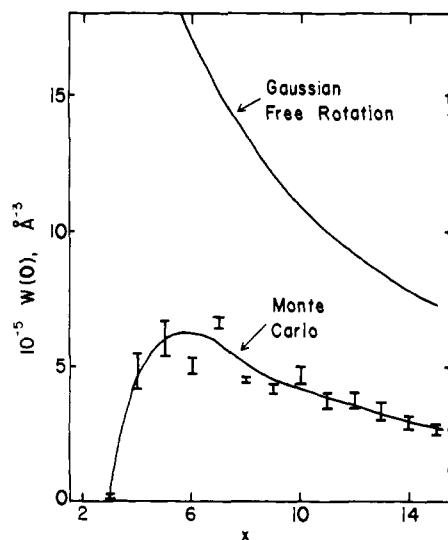
Figure 3. $W(O)$ as a function of x. Monte Carlo results were obtained using statistical weights evaluated with $E_\sigma = 900$ cal/mol, $E_{\sigma'} = -430$ cal/mol, $E_{\sigma''} = 2000$ cal/mol, and $E_\omega = 350$ cal/mol. $T = 298$ K.

Figure 4. A priori probability that bond i occupies the g^+ state for molecules with $x = 6$, $\Delta\theta$ no larger than $64°$, and Δr no larger than $0.36\langle r^2\rangle_{fr}^{1/2}$. Statistical weights are as in Figure 3. Remaining probabilities of interest can be obtained from $p_{g^+;i} = p_{g^-;i}$, $p_{t;i} = 1 - 2p_{g^+;i}$, and $p_{g^+;i} = p_{g^+;23-i}$. Dashed line denotes probabilities for the unperturbed open-chain analogue.

Results

Ease of Ring Closure. The ease of closing the ring for an open-chain analogue of any x is proportional to $W(O)$, where $W(r)$ is the probability per unit volume of the value r for the vector from "atom" 0 to "atom" n.[4] If $W(r)$ is Gaussian

$$W(O) = (3/2\langle r^2\rangle_{fr})^{3/2} \qquad (11)$$

where $\langle r^2\rangle_{fr}$ is the mean square end-to-end distance assuming free rotation.[4] Since $\langle r^2\rangle_{fr}$ increases with x, this expression predicts that $W(O)$ should decrease continuously as x increases. Figure 3 depicts the dependence of $W(O)$ on x if $W(r)$ is assumed to be Gaussian and $\langle r^2\rangle_{fr}$ is used.

Molecules with x in the range of interest will have a $W(r)$ which may be decidedly non-Gaussian owing to the small number of internal bonds and restricted rotation.[1,4] Under such circumstances, $W(O)$ may be estimated by recourse to Monte Carlo methods. Assuming spherical symmetry

$$W(r) \, dr = 4\pi r^2 \, W(r) \, dr \qquad (12)$$

where $W(r)$ is the probability that the end-to-end vector has length r. From the representative sample of N chains is obtained.

$$W(r) \, \Delta r = (N_{r+\Delta r} - N_r)(N\Delta r)^{-1}\Delta r \qquad (13)$$

where $N_{r+\Delta r} - N_r$ is the number of chains whose end-to-end distance lies between r and $r + \Delta r$. Combination of eq 12 and 13, with $r = 0$, yields

$$W(O) = \lim_{\Delta r \to 0} (N_{\Delta r}/N)(4\pi r^2 \Delta r)^{-1}$$

$$= \lim_{\Delta r \to 0} (N_{\Delta r}/N)[4\pi(\Delta r)^3/3]^{-1} \qquad (14)$$

where r^2 is the average of r^2 from 0 to Δr. If Δr is made too small, $W(O)$ will be subject to a large uncertainty. This uncertainty arises because $N_{\Delta r}/N$ becomes difficult to evaluate accurately at vanishingly small Δr unless N is made infinitely large.

The $W(O)$ reported here are based on eq 14 and computations performed with $\Delta r = a\langle r^2\rangle_{fr}^{1/2}$, where a was 1/4 and 1/2 for x less than 6. For larger x, a was 1/2 and 1. The number of chains generated at each x ranged from 25 000 to 80 000. They were divided into three to five sets, and error bars reflect $\pm$ one standard deviation for all sets of a given x. Results
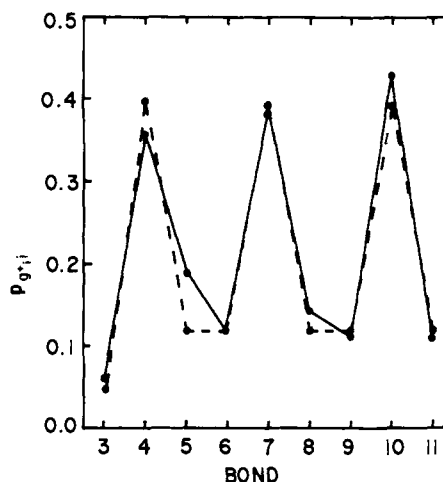
at 25 °C are depicted in Figure 3. They differ from the Gaussian, free rotation result (eq 11) in being lower and exhibiting a maximum. The chain with $x - 2$ has $W(O) = 0$, thus indicating an inability to close the ring. At $x = 3$, $W(O)$ becomes marginally greater than zero; therefore cyclization would be expected to be difficult. In the remaining cases examined ($x = 4$–15), $W(O)$ is of significant size. A maximum occurs with x in the vicinity of 5–7, and a monotonic decrease in $W(O)$ occurs as x increases above 7.

Polyoxyethylene Conformations Consistent with Cyclization. Figure 4 presents $p_{g^+;i}$ ($= p_{g^-;i}$) for bonds 3–11 in the molecule with $x = 6$. Symmetry dictates that $p_{g^+;i} = p_{g^+;23-i}$, and $p_{t;i}$ can be obtained as $1 - 2p_{g^+;i}$. The dashed line denotes probabilities for the open-chain analogue, obtained using eq 7 and 8. It demonstrates a pronounced tendency for gauche placements at C–C bonds, while trans placements are preferred at C–O bonds.

Rotational states adopted by bonds in the polyoxyethylene chain in the cyclic compound were obtained by examination of chains selected from an initial set of 99 999 representative open-chain analogues. Tolerances on Δr and $\Delta\theta$ were adjusted so that about 100 chains would survive the criteria for cyclization. Use of $\Delta\theta = 64°$ and $\Delta r = 0.36\langle r^2\rangle_{fr}^{1/2}$ permitted survival of 110 chains. Numerous conformations are adopted by the polyoxyethylene segments in the surviving molecules. The probability of g^+ placements is denoted by the solid line in Figure 4. This curve bears a strong resemblance to that obtained with the open-chain analogue. Cyclization at $x = 6$ does not require gross distortion of the inherent tendency of each bond to occupy t, g^+, and g^- states. The most important change arising as a consequence of cyclization is an increase in the probability of gauche placements at bonds 5 and 18.

Temperature Dependence of φ_1. The dihedral angle φ_1 is specified by the orientation of l_n with respect to the plane defined by l_1 and l_2. We shall define φ_1 as

$$\varphi_1 = \cos^{-1}\{(y_{n-1} - y_n)[(y_n - y_{n-1})^2 + (z_n - z_{n-1})^2]^{-1/2}\} \qquad (15)$$

where y_i, z_i are the y, z coordinates of atom i. The coordinate system in which y_i and z_i are expressed is defined by l_1 and l_2. Its x axis lies along, and in the direction of, l_1. The y axis is in the plane defined by l_1 and l_2, and oriented so that it has a positive projection on l_2. The z axis completes a right-handed Cartesian coordinate system. These definitions yield $\varphi_1 = 0°$

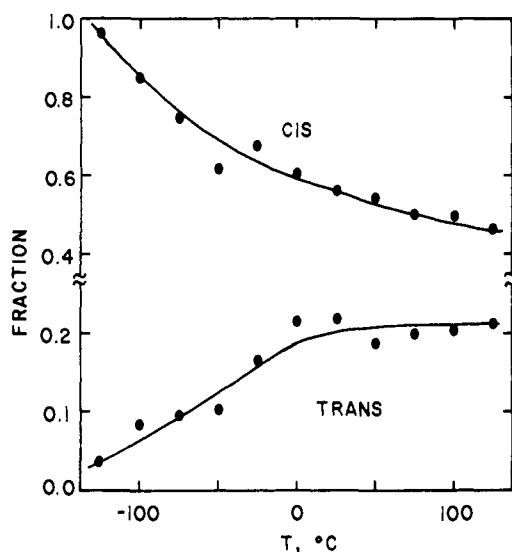**Figure 5.** Temperature dependence of the fraction of cyclic molecules with $\varphi_1 = 0 \pm 45°$ ("cis") and $\varphi_1 = 180 \pm 45°$ ("trans"), $x = 6$. Tolerances for Δr and $\Delta\theta$ are as in Figure 4, and energies are those used in Figures 3 and 4. Note the change in scale for the ordinate.

Figure 6. Representative conformations of the macrocycle with $x = 6$ (hydrogen atoms omitted). (A) φ_1 "cis," yielding a short end-to-end distance for the polyoxyethylene segment. (B) φ_1 "trans," yielding a longer end-to-end distance for the polyoxyethylene segment.

if there is a cis placement about the bond between the two rings, while $\varphi_1 = 180°$ if the placement is trans.

Computations for the molecule with $x = 6$ were carried out as described in the previous section, using statistical weights appropriate for temperatures in the range ± 125 °C. A total of 99 999 chains was generated at each temperature. Figure 5 depicts the temperature dependence of φ_1 for chains satisfying the tolerances for Δr and $\Delta\theta$ used above. At room temperature roughly 60% of the selected chains have $\varphi_1 = 0\text{--}45°$ ("cis"), while 20% have $\varphi_1 = 145\text{--}180°$ ("trans"). Cooling causes a decline in the "trans" population and an increase in "cis". At sufficiently low temperature, successful cyclization is achieved only when the state for φ_1 is "cis".

Changes in φ_1 with temperature are consistent with the sign of the temperature dependence of the unperturbed dimensions of polyoxyethylene. The mean square unperturbed end-to-end distance, $\langle r^2 \rangle_0$, of polyoxyethylene increases slightly upon heating, with d ln $\langle r^2 \rangle_0 / dT = 0.23\ (\pm 0.02) \times 10^{-3}\ \text{deg}^{-1}$.[6] Separation of the oxygen atoms bonded to the pyridine rings in the cyclic molecule is greater when $\varphi_1 = 180°$ (8.42 Å) than when $\varphi_1 = 0°$ (6.94 Å). Contraction of the polyoxyethylene fragment on cooling therefore leads to an increased preference for a "cis" placement at the bond between the rings.

Part of the polyoxyethylene chain must lie across the face of the aromatic system when φ_1 is "trans", but the polyoxyethylene fragment may be comparatively remote from the aromatic system when φ_1 is "cis". This situation is depicted
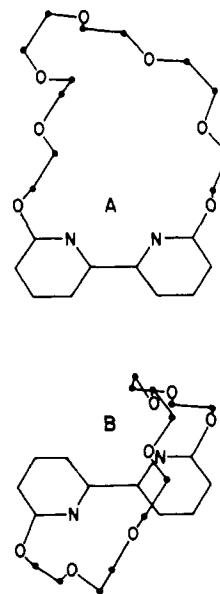
Figure 6, which shows two representative chains with C, N, and O atomic positions projected into the plane of the aromatic system. Most of the polyoxyethylene fragment actually lies out of this plane. Ring current effects on the protons in the polyoxyethylene moiety will differ substantially for these two conformations. The temperature dependence of the polyoxyethylene NMR spectrum arises from thermal alteration in the values of φ_1 adopted. The alteration of φ_1 in turn has its origin in the temperature dependence of the conformations adopted by the polyoxyethylene fragment.

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