Synthesis, Structure, and NMR Characterization of a Novel [3.3] Metacyclophane

Timothy J. Doyle and John Haseltine*

School of Chemistry and Biochemistry, Georgia Institute of Technology, Atlanta, Georgia 30332-0400

Received December 22, 1993
Revised July 18, 1994

The synthesis and crystal structure of metacyclophane **2** are reported. The nmr data relevant to conformational properties are also presented.

J. Heterocyclic Chem., **31**, 1417 (1994).

Cyclophanes have stimulated considerable interest because of their unique structural and dynamic properties [1]. The conformational space available to metacyclophanes is typically described in terms of syn and anti conformers and their interconversion pathways. Relative conformational energies are influenced by the length, hybridization, and substitution of the cyclophane bridges [2].

We would like to use tethered bis-imidazole substructures, represented by **1**, as hydrogen bonding domains within molecular receptors. The conformational preferences of **1** will determine in part the suitability of such receptors for particular purposes. In this context we have prepared the novel metacyclophane **2**. We report here the synthesis and crystal structure of **2** as well as ^{1}H nmr data relevant to conformational bias and mobility.

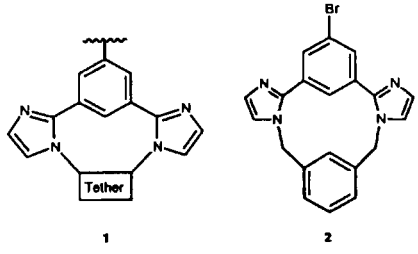

Figure 1.

The synthesis of **2** was accomplished in six steps by the sequence shown in Figure 2. Conversion of 5-bromoisophthalic acid [3] to the corresponding bis-carboxamide **4** was achieved in 84% yield. Polyphosphate ester (PPE) [4] in chloroform dehydrated **4** to yield dinitrile **5** in 85% yield [5]. Heating **5** with ethylenediamine in the presence of a catalytic amount of sulfur provided a 79% yield of bis-imidazoline **6** [6]. Subsequent exposure of **6** to Swern conditions effected conversion to bis-imidazole **7** in 36% yield [7]. Finally, alkylation of the sodium dianion of **7** with α,α'-dibromo-*m*-xylene [8] in dimethylformamide under conditions of high dilution provided **2** in yields ranging from 20 to 40%.

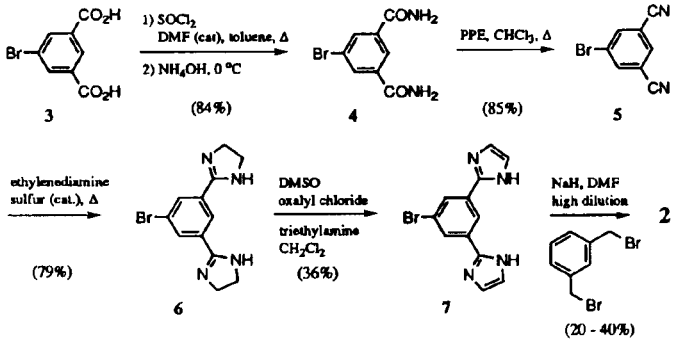

Figure 2. Synthesis of cyclophane **2**.

As shown by the computer generated ORTEP diagram (Figure 3), **2** crystallizes in the anti conformation. The structure presents no marked distortions from typical bond lengths. The sp^3 benzylic carbon atoms exhibit C-C-N bond angles of 112.5(14) and 113.4(14) degrees. The

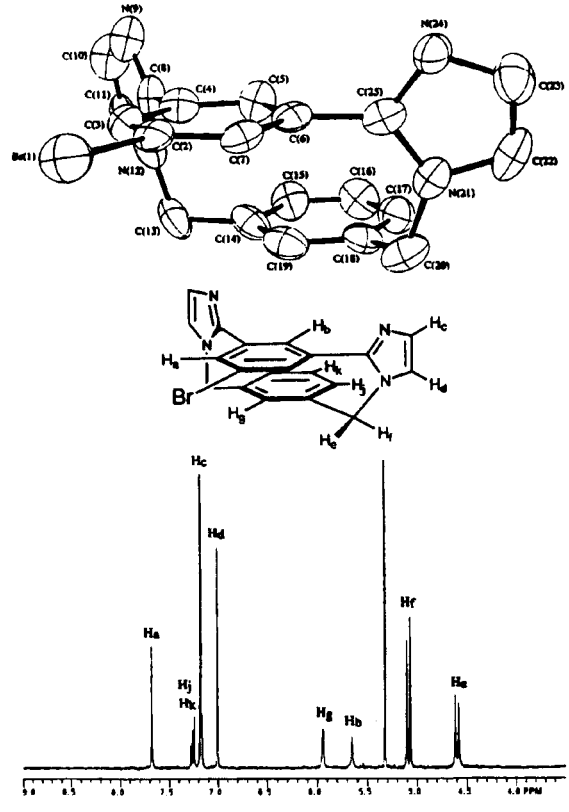

Figure 3. ORTEP plot and 400 MHz proton nmr spectrum (dichloromethane-d_2, rt) of cyclophane **2**.

Table 1

Crystal and Refinement Data for **2**

formula	$C_{20}H_{15}Br_4$
crystal system	orthorhombic
space group	P c a21
a, Å	18.712 (4)
b, Å	4.8827 (9)
c, Å	18.166 (6)
V Å3	1659.74
Z	4
formula weight	391.02
F (000)	848.00
density (calc), g/cm^3	1.565
crystal dim., mm	0.48 x 0.48 x 0.20
μ, absorption coef., mm^{-1}	2.46
2Theta (max), deg.	60.0
unique data	2482
unique data, $F_o > 2.5\sigma(F_o)$	1281
parameters refined	225
weight modifier K, in KF_o^2	0.0030000
R_f [a]	0.055
R_w [b]	0.074
GoF [c]	1.082

[a] $R_f = \Sigma(F_o-F_c)/\Sigma(F_o)$. [b] $R_w = [\Sigma(w(F_o-F_c)^2)/\Sigma(wF_o^2))]^{0.5}$. [c] GoF = $[\Sigma(w(F_o-F_c)^2)/(\text{No. of reflections - No. of parameters})]^{0.5}$

Table 2

Bond Lengths (Å) and Bond Angles (deg) for **2**

Br (1) - C (2)	1.855 (13)	C (13) - C (14)	1.49 (3)
C (2) - C (3)	1.358 (20)	C (14) - C (15)	1.412 (23)
C (3) - C (4)	1.406 (20)	C (15) - C (16)	1.39 (3)
C (4) - C (5)	1.400 (22)	C (16) - C (17)	1.34 (3)
C (5) - C (6)	1.362 (21)	C (17) - C (18)	1.41 (3)
C (6) - C (7)	1.373 (23)	C (18) - C (19)	1.40 (3)
C (7) - C (2)	1.391 (21)	C (18) - C (20)	1.51 (3)
C (4) - C (8)	1.485 (19)	C (20) - N (21)	1.463 (24)
C (8) - N (9)	1.32 (3)	N (21) - C (22)	1.359 (22)
N (9) - C (10)	1.379 (19)	C (22) - C (23)	1.34 (3)
C (10) - C (11)	1.33 (3)	C (23) - N (24)	1.387 (22)
C (11) - N (12)	1.374 (23)	N (24) - C (25)	1.322 (19)
N (12) - C (8)	1.355 (20)	C (25) - N (26)	1.362 (19)
N (12) - C (13)	1.47 (3)		
Br(1) - C (2) - C (3)	120.4 (11)	C (14) - C (19) - C (18)	124.4 (16)
C (2) - C (3) - C (4)	119.7 (13)	C (13) - C (14) - C (19)	122.7 (16)
C (3) - C (2) - C (7)	121.7 (12)	C (14) - C (15) -C (16)	119.0 (16)
C (3) - C (4) - C (5)	118.1 (13)	C (15) - C (14) - C (19)	117.6 (17)
C (4) - C (5) - C (6)	120.9 (14)	C (15) - C (16) - C(17)	121.7 (16)
C (5) - C (6) - C (7)	121.0 (15)	C (16) - C (17) - C (18)	121.6 (18)
C (6) - C (7) - C (2)	118.5 (13)	C (17) - C (18) - C(19)	115.6 (16)
C (6) - C (2) - Br(1)	117.9 (11)	C (17) - C (18) - C (20)	124.0 (16)
C (3) - C (4) - C (8)	120.0 (14)	C (19) - C (18) - C (20)	120.2 (16)
C (5) - C (4) - C (8)	121.9 (13)	C (18) - C (20) - N (21)	112.5 (14)
C (4) - C (8) - N (9)	123.3 (14)	C (20) - N (21) - C (22)	125.5 (14)
C (4) - C (8) - N (12)	124.5 (15)	C (20) - N (21) - C (25)	128.3 (13)
C (8) - N (9) - C (10)	103.7 (17)	C (22) - N (21) - C (25)	106.1 (14)
N (9) - C (10) - C (11)	111.7 (19)	N (21) - C (22) - C (23)	108.1 (15)
C (10) - C (11) - N (12)	105.9 (14)	C (22) - C(23) - N (24)	109.1 (16)
C (11) - N (12) - C (8)	106.5 (15)	C (23) - N (24) - C (25)	105.3 (14)
N (12) - C (8) - N (9)	112.1 (12)	N (24) - C (25) - N (21)	111.4 (14)
C (11) - N (12) - C (13)	125.0 (14)	N (24) - C (25) - C (6)	123.5 (13)
C (13) - N (12) - C (8)	128.4 (14)	N (21) - C (25) - C (6)	125.1 (13)
N (12) - C (13) - C (14)	113.4 (14)	C (25) - C (6) - C (7)	119.5 (13)
C (13) - C (14) - C (15)	119.5 (16)	C (25) - C (6)- C (5)	119.5 (14)

benzenoid rings are puckered in a manner which disposes C(5) and C(19) away from the cyclophane cavity. Each imidazole ring is canted somewhat, 7.3(15) and 6.3(15) degrees, from perfect orthogonality to the bromobenzene ring. The apical nitrogens, N(9) and N(24), are thus pointed slightly toward the bromine substituent.

Figure 3 also shows the 400 MHz proton nmr spectrum of **2** (dichloromethane-d_2, rt). The assignments are based upon a proton relayed COSY experiment. Both inner aryl protons (H_b and H_g) have chemical shifts in the range which is usually indicative of an anti conformation in cyclophanes [2e-h].

Table 3

Atomic Coordinates (x10^4) and Equivalent Isotropic Displacement Coefficients (Å^2 x 10^3) for **2**

	X	Y	Z	U(eq)
Br (1)	1116.8 (.8)	1102 (3)	2500.0	54.4 (0.5)
C (2)	650 (7)	-1560 (30)	1952 (7)	36 (4)
C (3)	-8 (7)	-2460 (30)	2158 (8)	39 (4)
C (4)	-340 (7)	-4570 (30)	1758 (8)	41 (5)
C (5)	21 (8)	-5650 (30)	1149 (8)	41 (5)
C (6)	661 (8)	-4590 (40)	931 (8)	34 (5)
C (7)	984 (7)	-2520 (30)	1319 (8)	38 (5)
C (8)	-1068 (7)	-5500 (30)	1965 (9)	41 (5)
N (9)	-1191 (6)	-7320 (30)	2491 (13)	54 (4)
C (10)	-1926 (8)	-7560 (40)	2497 (15)	66 (6)
C (11)	-2232 (8)	-5870 (40)	2013 (11)	64 (7)
N (12)	-1681 (6)	-4530 (30)	1667 (8)	50 (5)
C (13)	-1765 (10)	-2570 (40)	1061 (11)	62 (7)
C (14)	-1455 (8)	-3560 (30)	351 (10)	48 (6)
C (15)	-1793 (8)	-5710 (40)	-33 (9)	52 (6)
C (16)	-1464 (9)	-6790 (40)	-655 (10)	56 (6)
C (17)	-825 (12)	-5910 (40)	-883 (11)	56 (7)
C (18)	-460 (8)	-3800 (30)	-514 (10)	47 (5)
C (19)	-818 (9)	-2650 (30)	88 (10)	50 (6)
C (20)	296 (10)	-2920 (40)	-693 (10)	60 (6)
N (21)	828 (7)	-4940 (30)	-457 (6)	42 (4)
C (22)	1263 (9)	-6400 (40)	-911 (10)	57 (6)
C (23)	1693 (10)	-7940 (50)	-492 (10)	61 (7)
N (24)	1528 (7)	-7510 (30)	244 (7)	44 (4)
C (25)	1011 (7)	-5670 (30)	241 (9)	36 (4)

* Equivalent isotropic U defined as one third of the trace of the orthoganalized U_{ij} tensor.

Two mechanically different interconversions are possible between the syn and anti conformers of **2** (A and B in Figure 4). Interconversion A involves rotation of the bromobenzene ring about the bonds x_1 and x_2; interconversion B involves rotation of the xylylene ring about the bonds y_1 and y_2. Both of these processes must occur, either consecutively or in concert, in order to make all four benzylic protons magnetically equivalent. From the spectrum shown, the benzylic protons are clearly non-equivalent (H_e *vs.* H_f) at room temperature. Determination of the coalescence temperature for the benzylic protons would allow a calculation of the rate constant and activation energy of the coalescence process [9]. Therefore, 300

MHz spectra were recorded for a dimethyl sulfoxide-d_6 solution of **2** at 313, 333, 353, 373, 375, and 378K. The benzylic resonances were found to coalesce at 375K; this corresponds to a rate constant $k_{375} = 467\ s^{-1}$ and an activation energy of 18 kcal/mol.

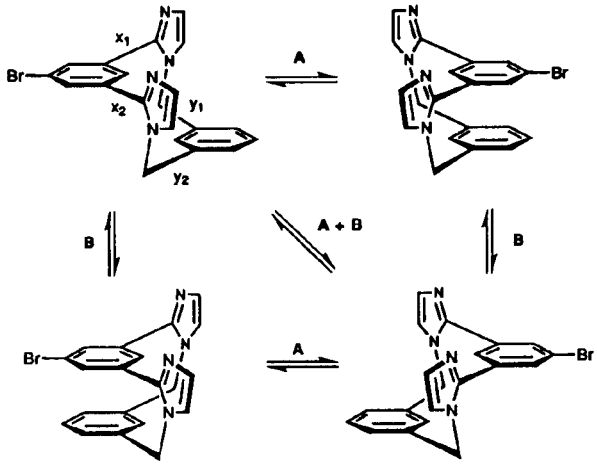

Figure 4. Interconversion pathways between syn and anti conformers of cyclophane **2** (bridge bond lengths are exaggerated for clarity of connectivity.

Although both interconversions **A** and **B** must occur to make the benzylic protons equivalent, and the net process is slow at room temperature, it is possible that one of the two steps is rapid at room temperature. In an attempt to detect a rapid interconversion step, the 300 MHz spectrum of **2** in dichloromethane-d_2 was recorded at 185K. However, at this temperature no additional resolutions were observed and the chemical shift difference between the benzylic resonances was only slightly altered ($\Delta\nu_{185K}$ = 0.52 ppm; $\Delta\Delta\nu$ = 0.04 ppm). If a process which is rapid at room temperature is sufficiently retarded at 185K, a change in the spectrum at the lower temperature should be evident. Our result suggests that there is no rapid process occurring at room temperature, and therefore that only a single conformer is significantly populated in the solution state.

A room temperature NOESY experiment was performed at 400 MHz (dichloromethane-d_2) in order to identify this conformer as syn or anti. The observed Overhauser enhancements are between H_g and H_f, H_g and H_e, and H_f and the multiplet region around 7.2 ppm. These enhancements are conceivable for either the syn or anti conformer. The lack of observed enhancements between H_b and H_g and H_a and H_j is consistent with the anti conformer.

In summary, we find that **2** can crystallize in an anti conformation, and although a single conformation appears to predominate in solution, its precise identity is less readily apparent. We are examining the utility of **2** as a hydrogen bonding domain in molecular receptors. These binding experiments should provide more information as to the conformational profile of this cyclophane substructure.

EXPERIMENTAL

Melting points were determined on a Meltemp apparatus from Laboratory Devices and are uncorrected. The infrared spectra were recorded on a Nicolet 520 FT-IR spectrometer. The 300 MHz ^1H spectra were recorded on a Varian Gemini 300 FT-NMR spectrometer. The 400 MHz ^1H spectra were recorded on a Varian XL-400 FT-NMR spectrometer. The high resolution mass spectra were recorded on a VG Instruments 70-SE mass spectrometer. The elemental analyses were performed by Robertson Microlit Laboratories, Inc., Madison, NJ.

5-Bromo-1,3-benzenedicarboxamide (**4**).

Thionyl chloride (4.54 ml, 7.40 g, 62.2 mmoles) was added dropwise over ten minutes to a stirred suspension of 6.10 g (24.9 mmoles) of 5-bromoisophthalic acid [3] in 20 ml of toluene and 0.5 ml of dimethyl formamide at room temperature. The resulting suspension was heated at reflux for 3.5 hours, during which time the suspension became a solution. The acid chloride solution was cooled to 0° and then cannulated into a flask containing 50 ml of concentrated ammonium hydroxide solution stirred at 0°. The resulting mixture was stirred at 0° for ten minutes and then allowed to return to room temperature while stirring for an additional hour. The mixture was filtered and the precipitate washed with water. The precipitate was crystallized from hot glacial acetic acid to give 5.06 g (84%) of **4** as fine white needles, mp 293-294° dec; ir (potassium bromide): 3400, 3221, 1663, 1378, 1095, 758, 667, 618 cm^{-1}; ^1H nmr (300 MHz, dimethyl sulfoxide-d_6): δ 7.60 (br s, 2 H), 8.17 (br s, 4 H), 8.35 (s, 1H); hrms: (ei, 1.3V) m/z Found: 241.9687. (M^+ Calcd. for $C_8H_7BrN_2O_2$: 241.9691.

5-Bromo-1,3-benzenedicarbonitrile (**5**).

Dicarboxamide **4** (25.0 g, 103 mmoles) and 211 g (488 mmoles) of polyphosphate ester [4] in 75 ml of chloroform were stirred at reflux for 16 hours. The reaction mixture was carefully poured into 300 ml of 30% potassium carbonate solution and the resulting mixture stirred for 30 minutes. The mixture was extracted with chloroform (3 x 100 ml). The combined extracts were washed with water (50 ml) followed by brine (50 ml). The organic phase was dried over sodium sulfate and concentrated. The resulting solid was crystallized from chloroform to give 18.1 g (85%) of **5** as fine white needles, mp 128-130°; ir (potassium bromide): 3079, 2236, 1563, 1415, 1244, 1105, 887, 813, 669 cm^{-1}; ^1H nmr (300 MHz, deuteriochloroform): δ 7.92 (d, J = 1.5 Hz, 1 H), 8.04 (d, J = 1.5 Hz, 2 H); hrms: (ei, 1.3V) m/z Found: 205.9482. M^+ Calcd. for $C_8H_3BrN_2$: 205.9480.

Anal. Calcd. for $C_8H_3BrN_2$: C, 46.41; H, 1.46; N, 13.53. Found: C, 46.21; H, 1.37; N, 13.34.

2,2'-(5-Bromo-1,3-phenylene)bis[4,5-dihydroimidazole] (**6**).

Dicarbonitrile **5** (3.20 g, 15.5 mmoles), sulfur (0.25 g, 7.8 mmoles), and 20 ml of ethylenediamine were stirred at reflux for 12 hours. The reaction mixture was allowed to cool to room temperature, during which time **6** crystallized from the solution. The product was filtered and washed with water. The resulting crystals were recrystallized from boiling ethylenediamine to give 3.57 g (79%) of **6** as fine white needles, mp 250-252° dec; ir (potassium bromide): 3450, 3148, 2931, 2865, 1624, 1563, 1514, 1472, 1326, 1271, 984, 874, 711 cm^{-1}; ^1H nmr (300 MHz, dimethyl sulfoxide-d_6): δ 3.61 (br s, 8 H), 7.09 (br s, 2 H), 8.03

(d, J =1.5 Hz, 2 H), 8.31 (d, J =1.5 Hz, 1 H); hrms: (ei, 4.0V) m/z Found: 292.0302. M^+ Calcd. for $C_{12}H_{13}BrN_4$: 292.0324.

Anal. Calcd. for $C_{12}H_{13}BrN_4$: C, 49.16; H, 4.47; Br, 27.26; N, 19.11. Found: C, 49.24; H, 4.31; Br, 27.20; N, 19.20.

2,2'-(5-Bromo-1,3-phenylene)bisimidazole (**7**).

Oxalyl chloride (0.42 ml, 0.61 g, 4.8 mmoles) was added to 20 ml of methylene chloride and the resulting solution was cooled to -78°. A solution of 0.82 ml (0.90 g, 11.6 mmoles) of dimethyl sulfoxide in 3.0 ml of methylene chloride was added slowly to the oxalyl chloride solution over 5 minutes. The resulting solution was stirred at -78° for five minutes. Powdered **6** (1.0 g, 3.4 mmoles) was added portionwise over 5 minutes *via* an addition tube. The mixture was stirred at -78° for 10 minutes. Triethylamine (3.6 ml, 2.61 g, 25.8 mmoles) was added and the resulting mixture was allowed to warm to room temperature. The mixture was stirred at room temperature for 16 hours. The mixture was concentrated and the residue chromatographed using methanol/chloroform (1:9) as eluant. The product-containing fractions were concentrated and then dissolved in 1*N* hydrochloric acid solution. The solution was filtered through celite and then made basic with 3*N* sodium hydroxide solution. The precipitated product was collected by filtration, washed with water, and dried to give 0.36 g (36%) of **7** as a powder. Slow evaporation of a 1:1 chloroform:tetrahydrofuran solution provided **7** as fine, slightly yellow needles, mp >270° dec; ir (potassium bromide): 3064, 2910, 2798, 1553, 1477, 1447, 1111, 863, 747 cm^{-1}; ^1H nmr (300 MHz, dimethyl sulfoxide-d_6): δ 7.08 (s, 2 H), 7.30 (s, 2 H), 8.06 (s, 2 H), 8.58 (s, 1 H); hrms: (ei, 1.4V) m/z Found: 288.0033. M^+ Calcd. for $C_{12}H_9BrN_4$: 288.0011.

[3.3] Metacyclophane **2**.

A 100 ml three neck round-bottom flask was equipped with two 50 ml addition funnels and a nitrogen inlet. The flask was then charged with 50 ml of freshly distilled (calcium hydride) dimethyl formamide. In a separate flask, bis-imidazole **6** (0.335 g, 1.16 mmoles) was dissolved in 5.0 ml of dimethylformamide and sodium hydride (78.4 mg, 3.27 mmoles) was added. The resulting mixture was stirred for 10 minutes and then cannulated into one of the addition funnels. The flask and cannula were rinsed into the same addition funnel with 5.0 ml of dimethylformamide. The other addition funnel was charged with a solution of α,α'-dibromo-*m*-xylene [8] in 10.0 ml of dimethyl formamide. The two solutions were added to the reaction vessel at the same rate over 2 hours. The resulting solution was allowed to stir at room temperature for 16 hours. The reaction was poured into 300 ml of water and extracted with chloroform (4 x 50 ml). The combined organic phases were washed with brine, and then dried over magnesium sulfate. After filtering and concentrating, the residue was applied to a column of silica gel and chromatographed with methanol/ether (2:3) as eluant to give 181.9 mg (40%) of **2** as a powder. X-ray quality crystals of **2** were obtained by slow evaporation of a methanol/benzene solution, mp (dichloromethane/methanol, needles) >260°; ir (potassium bromide): 3142, 3111, 3069, 3034, 2944, l487, 1460, 1418, 1398, 1325, 1282, 1238, 1124, 880, 750, 730, 704 cm^{-1}; ^1H nmr (400 MHz, dichloromethane-d_2): δ 4.60 (d, J = 14 Hz, 2H), 5.09 (d, J = 14 Hz, 2H), 5.65 (s, 1H), 5.94 (s, 1H), 7.00 (d, J = 1.4 Hz, 2H), 7.18 (d, J =1.4 Hz, 2H), 7.17-7.28 (m, 3H), 7.68 (s, 2H); hrms: (ei, 5.7V) m/z Found: 390.0481. M^+ Calcd. for $C_{20}H_{15}BrN_4$: 390.0482.

Anal. Calcd. for $C_{20}H_{15}BrN_4$: C, 61.39; H, 3.86; N, 14.32. Found: C, 61.20; H, 3.94; N, 14.29.

Acknowledgment.

Acknowledgment is made to the Donors of The Petroleum Research Fund, administered by the American Chemical Society, for support of this research (grant # 25513-G4). We thank Dr. Donald VanDerveer for performing the x-ray structure determination of **2** and Dr. Les Gelbaum for his assistance with the nmr experiments.

REFERENCES AND NOTES

[1] For a review see: Cyclophanes; Part 1, P. M. Keehn and S. M. Rosenfeld, eds, Academic, New York, 1983.

[2a] K. Sako, T. Shinmyozu, H. Takemura, M. Suenaga and T. Inuza, *J. Org. Chem.*, **57**, 6536 (1992); [b] H. Sasaki and T. Kitagawa, *Chem. Pharm. Bull.*, **36**, 1593 (1988); [c] H. Sasaki and T. Kitagawa, *Chem. Pharm. Bull.*, **35**, 4747 (1987); [d] M. F. Semmelhack, J. J. Harrison, D. C. Young, A. Gutierrez, S. Rafii and J. Clardy, *J. Am. Chem. Soc.*, **107**, 7508 (1985); [e] R. H. Mitchell and K. S. Weerawarna, *Tetrahedron Letters*, **29**, 5587 (1988); [f] D. Krois and H. Lehner, *Tetrahedron*, **38**, 3319 (1982); [g] F. Vögtle and P. Neumann, *Angew. Chem., Int. Ed. Engl.*, **11**, 73 (1972); [h] R. H. Mitchell, *Can. J. Chem.*, **58**, 1398 (1980); [i] F. Vögtle and L. Schunder, *Chem . Ber.*, **102**, 2677 (1969).

[3] E. W. Crandall and L. Harris, *Org. Prep. Proced.*, **1**, 147 (1969).

[4] For the preparation of polyphosphate ester (PPE), see Fieser and Fieser, Reagents For Organic Synthesis, Vol **1**, pp 892-894.

[5] Y. Kanaoka, T. Kuga, and K. Tanizawa, *Chem. Pharm. Bull.*, **18**, 397 (1970).

[6] N. Sawa, S. Kishizoe, K. Nagai, M. Kuriyama, Y. Tsujino and T. Shimamura, Toho Rayon Company, Ltd., Japanese Patent 24,965('64); *Chem. Abstr.*, **62**, 11820 (1965).

[7] S. C. Zimmerman, K. D. Cramer, and A. A. Galan, *J. Org. Chem.*, **54**, 1256 (1989).

[8] Aldrich Chemical Company, Milwaukee, Wisconsin.

[9] The variable temperature data were analyzed as described in H. Friebolin, Basic One and Two Dimensional NMR Spectroscopy, VCH, Weinheim, Germany, 1991, pp 269-272.