**Note Added in Proof.** It has been recently reported (Einhorn, C.; Einhorn, J.; Luche, J.-L. *Tetrahedron Lett.* **1991**, *32*, 2771) that addition will compete with COOH deprotonation when alkyllithiums react with carboxylic acids. The initial addition product undergoes elimination of LiOH to a ketone which can then react with another molecule of the alkyllithium. In such cases the 1:1 stoichiometry required for titrimetry would obviously no longer be maintained, and the compounds along the competing reaction path, or their anions, would be colorless. We have now examined some of our titration end point solutions by HPLC and NMR and find less than 1% of alkylation products in the isolated crude material from pyreneacetic acid/BuLi titration. Therefore, the conclusions drawn in our titration paper remain valid.

**Registry No.** 1, 64709-55-3; 1 dianion, 136569-20-5; 2, 24463-15-8; *n*-BuLi, 109-72-8; *s*-BuLi, 598-30-1; *t*-BuLi, 594-19-4; LDA, 4111-54-0; MeMgI, 917-64-6; 1-Li-hexyne, 17689-03-1; 4-biphenylmethanol, 3597-91-9.

## Bimolecular Cyclization of 2-Fluoro-*N*-(hydroxyalkyl)benzamides. 2. Synthesis and Structural Characterization of 17- and 20-Membered Macrocycles[1]

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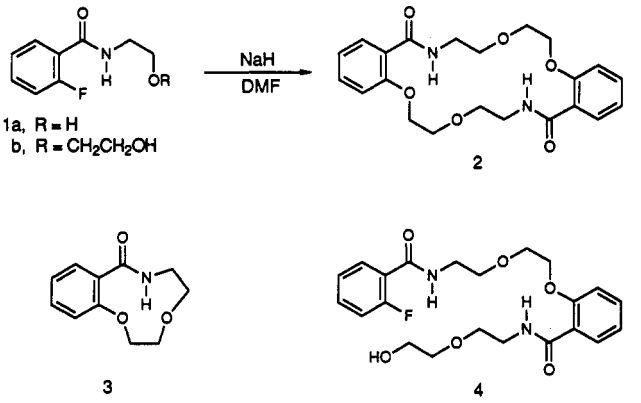
We have described a method for construction of macrocyclic diamides that involves a "one-step" bimolecular cyclization of 2-fluoro-*N*-(2-hydroxyalkyl)benzamides (e.g., **1a**).[1] The process was demonstrated in the context of 14-, 16-, and 18-membered ring synthesis. It is expected that this class of macrocycles will provide access to novel molecular receptors for a wide range of synthetic applications. In this paper we report an extension of the method to preparation of new heterocyclic systems containing 17- and 20-membered rings (e.g., **2** and **5**). It is demonstrated that **2** provides convenient access to novel tetraoxadiaza crown ethers **6a** and **6b**.

### Results and Discussion

As shown in Scheme I, treatment of a solution of 2-fluoro-*N*-[2-(2′-hydroxyethyl)ethoxy]benzamide (**1b**) in DMF (2.0 M) with sodium hydride (4 equiv) at 55 °C for 22 h gave 9,10:19,20-dibenzo-1,4,11,14-tetraoxa-7,17-diazacycloeicosane-8,18-dione (**2**) in 39% isolated yield; none of the 9,10-benzo-1,4-dioxa-7-azecin-8-one (**3**) could be detected. At lower starting concentrations of **1b** (0.01 M, 55 °C for 4 days) **2** was still produced (41%), but **3** also was obtained in 7% isolated yield. Utilization of milder reaction conditions (ambient temperature, 20 h) provided alcohol **4** (54% isolated yield) along with recovered starting material. It was shown that **4** gave macrocycle **2** on treatment with NaH in DMF.

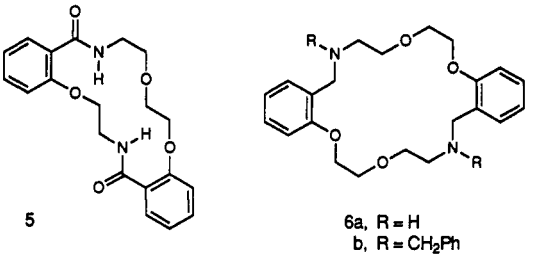
The isolation of **4** is of interest because in the earlier study directed at 14-membered ring formation,[1] no evidence for acyclic reaction intermediates could be obtained. This observation was suggestive of a template effect[3] in

**Scheme I**




which formation of the second bond was substantially faster than the first. Although the hypothetical template effect is kinetically less effective for the 20-membered ring synthesis, the yield of **2** is reasonable and oligomerization is not a problem, even at high concentrations of **1b** (e.g., 2 M).

Odd-numbered macrocyclic diamides are available in reasonable yield by a simple modification of the protocol for bimolecular cyclization. Thus, treatment of an equimolar mixture of **1a** and **1b** with NaH/DMF at ambient temperature for 4 days gave 9,10:16,17-dibenzo-1,4,11-trioxa-7,14-diazacycloheptadecane-8,15-dione (**5**) in 36% yield, along with **2** (12%), traces of the macrocycle derived from **1a**,[1] and recovered starting materials; macrocycle **5** was easily isolated by flash chromatography on silica gel.




Reduction of **2** with the borane–dimethyl sulfide complex in THF in the presence of boron trifluoride etherate gave the macrocyclic diamine **6a** in 93% yield. Dibenzylation of **6a** with benzyl bromide/NaH in THF gave the *N,N*-dibenzyl derivative **6b** (80%). X-ray crystallographic studies of **2** and **6b** provided the molecular structures shown in Figures 1 and 2.

In contrast to the 14-membered macrocycles[1] that display a butterfly-like conformation in the solid state, **2** assumes a bracket conformation with the aromatic rings in nearly parallel planes; the averaged planes of the aromatic rings in **2** intersect at an angle of 8.2°. The distance from an orthogonal projection from the plane defined by C(1)–C(2)–C(3)–C(4)–C(4a)–C(24a) to C(16a) is 2.37 Å while that to C(14) is 2.76 Å. Both NH groups are within the macrocyclic cavity, and, as a result, two weak intramolecular hydrogen bonds are possible.[4] The unconstrained H(11)–O(17) and H(23)–O(5) distances are 2.01 and 2.05 Å, respectively; N(11)–H(11)–O(17) and N(23)–H(23)–O(5) angles are 131 and 134°.

(1) For the first paper in this series, see: Schultz, A. G.; Pinto, D. J. P.; Welch, M.; Kullnig, R. K. *J. Org. Chem.* **1988**, *53*, 1372.

(2) Inquiries regarding the X-ray crystallographic analyses should be directed to F.S.T.

(3) (a) Busch, D. H. *Rec. Chem. Progr.* **1964**, *25*, 107. (b) Eschemoser, A. *Pure Appl. Chem.* **1969**, *20*, 1.

(4) (a) A similar amide orientation is present in the 14-membered analogues; see ref 1. (b) For the observation of "very weak" intramolecular hydrogen bonds in synthetic derivatives of the quinoxaline antibiotic triostin A, see: Hossain, M. B.; van der Helm, D.; Olsen, R. K.; Jones, P. G.; Sheldrick, G. M.; Egert, E.; Kennard, O.; Waring, M. J.; Viswamitra, M. A. *J. Am. Chem. Soc.* **1982**, *104*, 3401.

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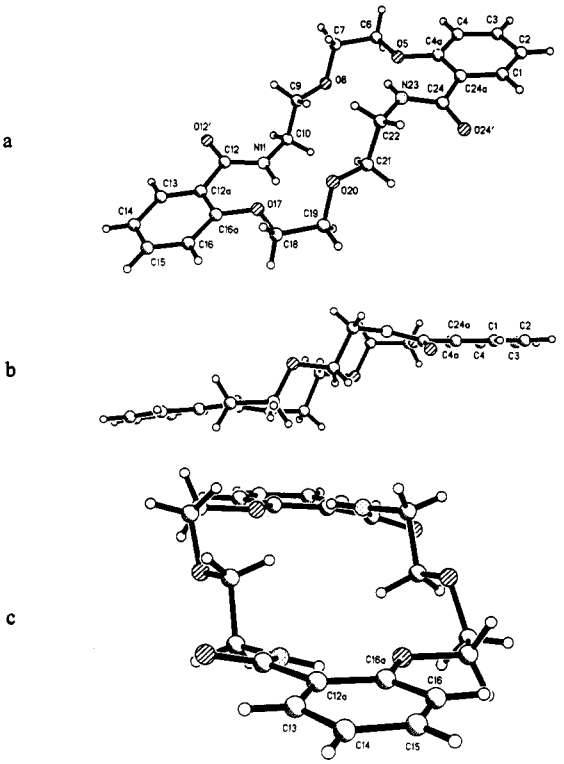

**Figure 1.** Molecular structure of **2**: (a) perspective view showing N–H bonds residing within macrocyclic cavity, (b) longitudinal view showing bracket shape, (c) end view showing distance between plane of top aromatic ring and C(16a) (2.37 Å) and C(14) (2.76 Å) of bottom aromatic ring.

The overall shape of the macrocyclic ring in **6b** is similar to that of **2**, except N,N-dibenzylation requires rotations about the bonds in the vicinity of N(11) and N(23) so that the benzyl substituents are able to reside outside the macrocyclic cavity in pseudoequatorial conformations. The benzo groups in **6b** are in parallel planes with a distance of 1.00 Å separating the planes. The rings of the *N,N*-dibenzyl substituents also are in parallel planes 9.26 Å apart.

It should be noted that the two-dimensional structure for **6a** is drawn as shown for convenience. On the basis of an earlier X-ray diffraction analysis of 6,7:13,14-dibenzo-1,8-dioxa-4,11-diazacyclotetradecane[1] it is suggested that the conformation of **6a** is similar to that of **2** with both NH groups situated within the macrocyclic cavity. Thus, by the simple expedient of N,N-disubstitution, it is possible to switch from one bracket conformation to another. This inside–outside conversion decreases the distance between planes of the benzo groups but maintains the general shape of the macrocyclic ring.

Although the scope of this report has been limited to synthesis and characterization of unsubstituted 17- and 20-membered ring systems, **2** and **5**, earlier work[1] suggests that a wide range of chiral 17- and 20-membered macrocycles will be available by appropriate modification of the intermediate 2-fluorobenzamide structure.

## Experimental Section

**General Procedures.** $^1$H NMR spectra were recorded at 200 MHz; tetramethylsilane was used as the internal standard. Analytical TLC were performed on silica gel F-254 plates. Solutions were concentrated by rotary evaporation. Residual solvent was removed by utilization of a mechanical vacuum pump.

**2-Fluoro-*N*-[2-(2′-hydroxyethyl)ethoxy]benzamide (1b).** A mixture of 2-(2-aminoethoxy)ethanol (1.92 mL, 26.6 mmol) in $CH_2Cl_2$ (29 mL) and aqueous NaOH (10%, 10 mL) was cooled (0 °C) in an ice bath. To this vigorously stirred solution was added

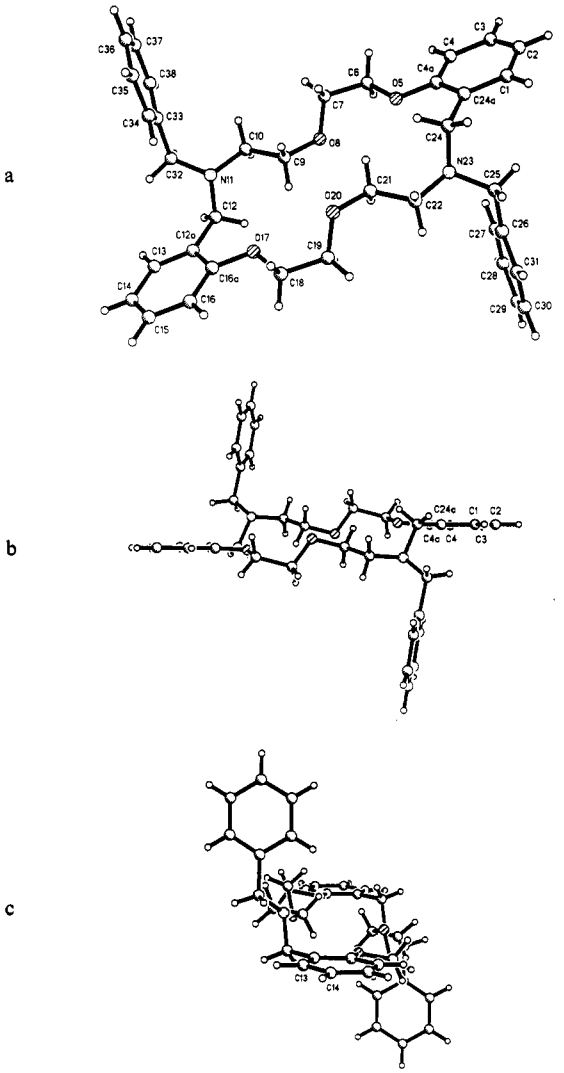

**Figure 2.** Molecular structure of **6b**: (a) perspective view showing altered shape of macrocyclic cavity relative to perspective view of **2**, (b) longitudinal view showing the *N*-benzyl substituents in parallel planes 9.26 Å apart, (c) end view showing distance (1.00 Å) separating benzo groups that are in parallel planes.

a solution of 2-fluorobenzoyl chloride (3.0 mL, 25 mmol) in $CH_2Cl_2$ (39 mL) over 0.5 h. The mixture was then allowed to warm to ambient temperature, and stirring was continued for 2 h. $H_2O$ (40 mL) was added, and the organic layer was separated. The aqueous layer was washed with $CH_2Cl_2$ (2 × 20 mL), and the combined organic extracts were washed with brine (20 mL) and dried ($MgSO_4$). Removal of the solvent in vacuo gave an oil which was chromatographed on silica gel (5:4 ethyl acetate/hexane) to afford **1b** as a pale yellow oil (3.77 g, 66%) and the 2-fluorobenzoate derivative of **1b** as a colorless oil (0.88 g, 10%). **1b**: $R_f$ = 0.74; $^1$H NMR ($CDCl_3$) δ 2.94 (br s, 1 H), 3.52 (m, 2 H), 3.59 (s, 4 H), 3.66 (m, 2 H), 6.96–7.42 (m, 4 H), 7.93 (dt, $J_d$ = 2 Hz, $J_t$ = 8 Hz, 1 H); IR (film) 3400, 1650 cm$^{-1}$; CIMS *m/z* (relative intensity) 228 ($M^+$ + 1, 20). Anal. Calcd for $C_{11}H_{14}O_3NF$: C, 58.14; H, 6.21. Found: C, 58.03; H, 6.28.

The 2-fluorobenzoate of **1b**: $R_f$ = 0.41; $^1$H NMR ($CDCl_3$) δ 3.73 (s, 4 H), 3.84 (m, 2 H), 4.51 (m, 2 H), 6.95–7.26 (m, 4 H), 7.37–7.55 (m, 2 H), 7.92 (dt, $J_d$ = 2 Hz, $J_t$ = 8 Hz, 1 H), 8.06 (dt, $J_d$ = 2 Hz, $J_t$ = 8 Hz, 1 H).

To a solution of the 2-fluorobenzoate (1.70 g, 4.87 mmol) in $CH_3OH$ (16 mL) was added 1 M NaOH (5.6 mL). The resulting clear yellow solution was stirred for 5 h, acidified with 1 M HCl (6 mL), diluted with $H_2O$ (20 mL), and washed with $CH_2Cl_2$ (5 × 20 mL). The combined organic extracts were washed with saturated $NaHCO_3$ (10 mL) and dried ($MgSO_4$). Removal of the solvent in vacuo afforded **1b** as a pale yellow oil (1.01 g, 91%).

**9,10:19,20-Dibenzo-1,4,11,14-tetraoxa-7,17-diazacycloeicosane-8,18-dione (2).** A solution of **1b** (60 mg, 0.26 mmol) and

NaH (25 mg, 1.1 mmol) in DMF (0.52 mL) was stirred at 55 °C for 22 h. To the cooled solution was added 1 mL of $H_2O$ and 0.9 mL of 1 M HCl (pH of resulting solution ~7). The aqueous solution was washed with $CH_2Cl_2$ (5 × 2 mL), and the combined organic extracts were washed with brine (10 mL) and dried ($MgSO_4$). The solvent was removed in vacuo to give a yellow solid, which was chromatographed on silica gel (20:1 ethyl acetate/methanol) to afford **2** as colorless crystals (20.7 mg, 39%): mp 177–9 °C; $^1H$ NMR ($CDCl_3$) δ 3.69 (m, 4 H), 3.76 (m, 4 H), 3.84 (m, 4 H), 4.22 (m, 4 H), 6.94 (d, $J$ = 7.8 Hz, 2 H), 7.07 (dt, $J_d$ = 1 Hz, $J_t$ = 7.7 Hz, 2 H), 7.40 (dt, $J_d$ = 2 Hz, $J_t$ = 7.8 Hz, 2 H), 8.15 (dd, $J$ = 2 Hz, $J$ = 7.8 Hz, 2 H), 8.70 (bs, 2 H); IR ($CHCl_3$) 3395, 1645 cm$^{-1}$; CIMS $m/z$ (relative intensity) 415 ($M^+$ + 1, 100). Crystals of **2** suitable for X-ray crystallographic studies were obtained from hexanes/$CH_2Cl_2$ (1:1) by the isothermal distillation technique, mp 185–186.5 °C. Anal. Calcd for $C_{22}H_{26}N_2O_6$: C, 63.76; H, 6.32. Found: C, 63.52; H, 6.35.

**9,10-Benzo-1,4-dioxa-7-azecin-8-one (3).** A solution of **1b** (50 mg, 0.22 mmol) and NaH (60% in oil, 35 mg, 0.88 mmol) in DMF (22 mL) was stirred at 55 °C for 4 days. The solvent was removed in vacuo and the brown residue was dissolved in $H_2O$ (10 mL) and neutralized with 1 M HCl (0.9 mL). The aqueous solution was washed with $CH_2Cl_2$ (3 × 15 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated to give a light brown oil. Flash chromatography (silica gel, 6:1 $CH_2Cl_2$/acetonitrile) afforded **3** as colorless crystals (3.0 mg, 7%) and **2**. Preparative TLC of **2** so obtained (6:1 $CH_2Cl_2$/acetonitrile) afforded colorless crystals (18.5 mg, 41%). **3**: mp 99–102 °C; $^1H$ NMR ($CDCl_3$) δ 3.62 (overlapping t's, $J$ = 5.4, 6.2 Hz, 2 H), 3.76 (overlapping d's, $J$ = 5 Hz, 2 H), 3.87 (overlapping d's, $J$ = 4.1, 4.5 Hz, 2 H), 4.07 (overlapping d's, $J$ = 4.4, 5.0 Hz, 2 H), 7.15 (dd, $J$ = 1.2, 7.9 Hz, 1 H), 7.26 (dt, $J_d$ = 1.2 Hz, $J_t$ = 8.1 Hz, 1 H), 7.45 (dt, $J_d$ = 1.9 Hz, $J_t$ = 7.7 Hz, 1 H), 7.71 (br s, 1 H), 7.85 (dd, $J$ = 1.9, 7.6 Hz, 1 H); IR ($CHCl_3$) 3455, 1655 cm$^{-1}$; CIMS $m/z$ (relative intensity) 208 ($M^+$ + 1, 100). Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32. Found: C, 63.88; H, 6.48.

**Isolation of 4 and Conversion to 2.** A solution of **1b** (250 mg, 1.10 mmol) in DMF (5.5 mL) was added to a solution of NaH (60% in oil, 132 mg, 3.30 mmol) in DMF (5.5 mL), and the mixture was stirred for 20 h. The DMF was removed in vacuo, and the brown residue was dissolved in $H_2O$ (20 mL). The aqueous layer was washed with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with brine (30 mL) and then dried ($MgSO_4$). Removal of the solvent in vacuo and flash chromatography (silica gel, 4:3 hexane/acetone) afforded **1b** (40 mg, 16%) and **4** (123 mg, 54%) as a colorless syrup: $^1H$ NMR ($CDCl_3$) δ 1.95 (br s, 1 H), 3.52–3.62 (m, 6 H), 3.65–3.82 (m, 6 H), 3.90–3.96 (m, 2 H), 4.23–4.35 (m, 2 H), 6.9–7.5 (m, 7 H), 8.0 (dt, $J_d$ = 2 Hz, $J_t$ = 8 Hz, 1 H), 8.19 (dd, $J$ = 2, 8 Hz, 1 H), 8.42 (br s, 1 H); IR ($CHCl_3$) 3470, 3400, 1650, 1620, 1605 cm$^{-1}$; desorption CIMS $m/z$ (relative intensity) 435 ($M^+$ + 1, 100). Anal. Calcd for $C_{22}H_{27}N_2O_6F$: C, 60.82; H, 6.26. Found: C, 60.89; H, 6.38.

To **4** (63 mg, 0.145 mmol) in DMF (0.6 mL) was added NaH (14 mg, 0.58 mmol), and the solution was warmed to 60 °C. After stirring for 20 h the mixture was cooled, diluted with $H_2O$ (10 mL), neutralized with 6 M HCl, and washed with $CH_2Cl_2$ (5 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated to afford 50.6 mg (84% yield) of **2**. Flash chromatography (3:2 benzene/acetonitrile) of the product gave 29.0 mg (48%) of **2**.

**9,10:16,17-Dibenzo-1,4,11-trioxa-7,14-diazacycloheptadecane-8,15-dione (5).** A solution of **1b** (124 mg, 0.55 mmol), **1a** (100 mg, 0.55 mmol), and NaH (26 mg, 1.1 mmol) in DMF (6.1 mL) was stirred for 4 days. The reaction mixture was diluted with $H_2O$ (20 mL) and neutralized with 1 M HCl, after which a colorless solid precipitated. The suspension was washed with $CH_2Cl_2$ (3 × 25 mL), and the combined organic extracts were dried ($MgSO_4$) and evaporated to afford a light brown solid. Flash chromatography on silica gel (3:1 benzene/acetonitrile) gave **5** (74 mg, 36%) along with recovered **1a** (12.6 mg, 10%) and **2** (13.5 mg, 12%). **5**: mp 184–7 °C; $^1H$ NMR ($CDCl_3$) δ 3.79 (m, 4 H), 3.95 (m, 4 H), 4.28 (m, 4 H) 6.95 (m, 2 H), 7.08 (t, $J$ = 8 Hz, 2 H), 7.42 (complex q, 2 H), 8.14 (dd, $J$ = 1.8, 7.7 Hz, 1 H), 8.20 (dt, $J_t$ = 1.6 Hz, $J_d$ = 7.8 Hz, 1 H), 8.35 (br s, 1 H), 8.85 (t, $J$ = 5.7 Hz, 1 H); IR ($CHCl_3$) 3410, 1645 cm$^{-1}$; CIMS $m/z$ (relative intensity) 371 ($M^+$ + 1, 45), 327 (100). Anal. Calcd for $C_{20}H_{22}N_2O_5$: C, 64.85; H, 5.99. Found: C, 64.78; H, 6.05.

**9,10:19,20-Dibenzo-1,4,11,14-tetraoxa-7,17-diazacycloeicosane (6a).** To a solution of **2** (135 mg, 0.33 mmol) in THF (33 mL) was added boron trifluoride etherate (0.10 mL, 0.82 mmol) and borane–dimethyl sulfide complex (0.07 mL, 10 M). The mixture was warmed to reflux and stirred for 1.5 h. The dimethyl sulfide was then removed by distillation. The remainder of the solution was refluxed for 6 h, the solvent was removed, and 10% KOH (10 mL) and MeOH (10 mL) were added. The solution was refluxed overnight, after which the organic solvents were removed in vacuo. The remaining aqueous solution was washed with $CH_2Cl_2$ (5 × 15 mL). The combined organic extracts were dried ($MgSO_4$), and solvent was evaporated to give a yellow solid. The solid was dissolved in $CH_2Cl_2$ (5 mL), the solution was washed with HCl (5 mL, 1 M) and dried ($MgSO_4$), and the solvent was evaporated to afford recovered **2** (10 mg, 7%). The aqueous layer was made basic with concentrated KOH until pH ~ 14. The resulting colorless suspension was washed with $CH_2Cl_2$ (3 × 5 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent was evaporated to afford **6a** as colorless crystals (118 mg, 93%): mp 260–2 °C dec; $^1H$ NMR ($CDCl_3$) δ 2.48 (s, 2 H), 2.78 (t, $J$ = 3.5 Hz, 4 H), 3.68 (t, $J$ = 3.5 Hz, 4 H), 3.79 (br s, 8 H), 4.06 (br s, 4 H), 6.80 (d, $J$ = 6.0 Hz, 2 H), 6.89 (t, $J$ = 5.5 Hz, 2 H), 7.19 (dt, $J$ = 1.0, 5.5 Hz, 4 H); IR ($CHCl_3$) 3325, 3000, 2935, 1600, 1595 cm$^{-1}$; CIMS $m/z$ (relative intensity) 387 ($M^+$ + 1, 100). An acceptable analysis could not be obtained.

**Preparation of 6b.** A solution of **6a** (50 mg, 0.13 mmol) and NaH (8 mg, 0.3 mmol) in THF (0.65 mL) was stirred for 10 min. Benzyl bromide (0.04 mL, 0.3 mmol) was added, and the mixture was stirred overnight, diluted with $H_2O$ (1 mL), and washed with $CH_2Cl_2$ (3 × 2 mL). The combined organic extracts were dried ($MgSO_4$), and the solvent was removed in vacuo. The light brown residue was chromatographed on silica gel (1:1 ethyl acetate/hexane) to afford **6b** as a light tan solid (58.8 mg, 80%); mp 106–8 °C; $^1H$ NMR ($CDCl_3$) δ 2.80 (t, $J$ = 6.3 Hz, 4 H), 3.67 (s, 4 H), 3.68 (d, $J$ = 6 Hz, 4 H), 3.76 (m, 4 H), 3.81 (s, 4 H), 4.07 (overlapping d's, $J$ = 4.4, 6 Hz, 4 H), 6.80 (dd, $J$ = 1.0, 7.2 Hz, 2 H), 6.91 (dt, $J_d$ = 1.0 Hz, $J_t$ = 7.4 Hz, 2 H), 7.1–7.4 (m, 14 H); IR ($CHCl_3$) 3000, 2920, 2865, 1595, 1585 cm$^{-1}$; CIMS $m/z$ (relative intensity) 567 ($M^+$ + 1, 2), 386 (3), 219 (51), 196 (23), 92 (64). Crystals of **6b** suitable for X-ray crystallographic studies were obtained from hexanes/$CH_2Cl_2$ (1:1) by the isothermal distillation technique, mp 110–1 °C. Anal. Calcd for $C_{36}H_{42}N_2O_4$: C, 76.30; H, 7.47. Found: C, 76.42; H, 7.51.

**Acknowledgment.** We thank the National Institutes of Health for financial support (Grant GM 26568).

**Registry No.** **1a**, 111904-31-5; **1b**, 136538-57-3; **2**, 136538-58-4; **3**, 136538-59-5; **4**, 136538-60-8; **5**, 136538-61-9; **6a**, 136538-62-0; **6b**, 136538-63-1; 2-(2-aminoethoxy)ethanol, 929-06-6; 2-fluorobenzoyl chloride, 393-52-2.

**Supplementary Material Available:** Tables of crystal structure data, atomic coordinates, bond angles, bond lengths, anisotropic parameters, and hydrogen atom coordinates for **2** and **6b** (16 pages). Ordering information is given on any current masthead page.

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## β-Secondary Deuterium Kinetic Isotope Effect for the Insertion of Dichlorocarbene into a C–H Bond

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*Received March 15, 1991*

Large normal α- and/or β-secondary deuterium and tritium kinetic isotope effects (KIEs) have been observed in several enzyme-catalyzed hydroxylations of aliphatic carbons[1-3] and are evidence of a degree of $sp^3$ to $sp^2$ re-

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