μm). All solvents used were purified and/or dried by standard methods.[22]

Ethyl 3,3-Dibromopyruvate (3). A solution of ethyl bromopyruvate (5.00 g, 25.6 mmol), *N*-bromosuccinimide (4.56 g, 25.6 mmol), and azobis(isobutyronitrile) (50 mg, catalytic) in CCl_4 (100 mL) was heated at reflux for 4 h with intermittent UV irradiation from a Minerallight UVSL-25 UV lamp. The 254 μm light was held directly on the side of the flask for 2 min every 10 min during the first 30 min of the reaction. The mixture was cooled and filtered to remove succinimide, and the filtrate was evaporated to give a yellow oil. Flash chromatography (35% EtOAc/hexanes) of the crude product gave 5.60 g (80% yield) of **3** as a colorless oil: ^{1}H NMR (270 MHz, D_2O) δ 6.03 (s, 1 H), 4.24 (q, J = 7.15 Hz, 2 H), 1.22 (t, J = 7.15 Hz, 3 H); exact mass 273.87 (273.87 calcd for $C_5H_6O_3{}^{79}Br^{81}Br$).

Ethyl (*Z*)-3-Bromo-2-[(dimethoxyphosphinyl)oxy]propenoate (4a) and Ethyl (*E*)-3-Bromo-2-[(dimethoxyphosphinyl)oxy]propenoate (4b). A refluxing solution of **3** (0.274 g, 1.00 mmol) in dioxane (5 mL) was treated all at once with trimethyl phosphite (0.144 g, 1.00 mmol), and the heating was continued for 30 min. The solvent was removed on a rotary vacuum evaporator (water aspirator/35 °C). The residual colorless oil was purified by flash chromatography (70% EtOAc/hexane) followed by MPLC (20% EtOAc/hexanes) to give 0.171 g (52% yield) of **4a** and 0.061 g of **4b** (20%) as colorless oils.[23] **4a**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.24 (d, J = 1.7 Hz, 1 H), 4.30 (q, J = 7.3 Hz, 2 H), 3.95 (d, J = 11.5 Hz, 6 H), 1.33 (t, J = 7.3 Hz, 3 H); exact mass 302.9626 (302.9633 calcd for $C_7H_{12}{}^{79}BrPO_6$). **4b**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.96 (d, J = 2.9 Hz, 1 H), 4.34 (q, J = 7.3 Hz, 2 H), 3.87 (d, J = 11.4 Hz, 6 H), 1.26 (t, J = 7.3 Hz, 3 H).

Ethyl (*Z*)-3-Deuterio-2-[(dimethoxyphosphinyl)oxy]propenoate (5a). Bromopyruvate **4a** (0.080 g, 0.264 mmol) in 20% D_2O/THF (the THF is predried and distilled as previously described)[22] (5 mL) was treated with freshly prepared Zn/Ag couple[18] (200 mg) doped with D_2O. The progress of the reaction was monitored via TLC (silica gel/40% EtOAc/hexanes). After all the starting material has been consumed (24 h), the couple is removed by filtration. The solid was washed with diethyl ether (3 × 5 mL). The ether layer was separated from the filtrate, dried (Na_2SO_4), and evaporated under reduced pressure to give colorless oil **5a** in quantitative yield (0.059 g): ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.96 (d, J = 2.4 Hz, 1 H), 4.28 (q, J = 7.3 Hz, 2 H), 3.88 (d, J = 11.4 Hz, 6 H), 1.33 (t, J = 7.3 Hz, 3 H); exact mass 225.05 (225.05 calcd for $C_7H_{12}DPO_6$).

Ethyl 3-Deuterio-3,3-dibromopyruvate (6). Ethyl dibromopyruvate (**3**) (1.00 g, 3.64 mmol) was dissolved in D_2O (25 mL), sodium bicarbonate (200 mg) was added, and the mixture was stirred overnight. Evaporation of the water layer (0.1 mm/35 °C) gave a yellowish emulsion, which was extracted with diethyl ether (3 × 10 mL). The ether layers were dried (Na_2SO_4) and evaporated to give yellow oil (1.00 g, 100% yield) **6**. The material was *not* purified by chromatography since this results in complete loss of the deuterium atom: ^{1}H NMR (270 MHz, D_2O) δ 4.24 (q, J = 7.1 Hz, 2 H), 1.22 (t, J = 7.1 Hz, 3 H); exact mass 274.88 (274.88 calcd for $C_5H_5DO_3{}^{79}Br^{81}Br$).

Ethyl (*Z*)-3-Bromo-3-deuterio-2-[(dimethoxyphosphinyl)oxy]propenoate (7a). In a procedure analogous to that used to convert **3** to **4a**, compound **6** (0.738 g, 2.68 mmol) was transformed to *Z* isomer **7a** (0.462 g) in 56% yield. The *E* isomer **7b** was obtained in 20% yield. **7a**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 4.30 (q, J = 7.3 Hz, 2 H), 3.95 (d, J = 11.5 Hz, 6 H), 1.33 (t, J = 7.3 Hz, 3 H); exact mass 303.97 (303.97 calcd for $C_7H_{11}D^{79}BrPO_6$). **7b**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 4.34 (q, J = 7.3 Hz, 2 H), 3.87 (d, J = 11.4 Hz, 6 H), 1.26 (t, J = 7.3 Hz, 3 H); exact mass 303.97 (303.97 calcd for $C_7H_{11}D^{79}BrPO_6$).

Ethyl (*E*)-3-Deuterio-2-[(dimethoxyphosphinyl)oxy]propenoate (5b). Compound **7a** (0.126 g, 0.45 mmol) was treated with a freshly prepared Zn/Ag couple (250 mg) doped with H_2O, in a manner similar to that reported above for the transformation of **4a** to **5a**, to give **5b** as a colorless oil (0.93 g, quantitative yield): ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.62 (d, J = 2.4 Hz, 1 H), 4.28 (q, J = 7.3 Hz, 2 H), 3.88 (d, J = 11.4 Hz, 6 H), 1.33 (t, J = 7.3 Hz, 3 H).

Acknowledgment. This work was supported by U.S. Public Health Service Grant GM 36184 and an Upjohn Starter Grant from the College of Pharmacy. We are grateful to the U.S.P.H.S. and the College of Pharmacy for their contribution to the purchase of the IBM 270-MHz NMR instrument. We wish to thank Ms. Stacie Tate, a participant in the NIH sponsored College of Pharmacy Summer Minority High School Apprenticeship Program, for her expert technical assistance in the purification of the **3**, **4a**, and **4b**.

Registry No. 1 R_1 = D, R^2 = H, 56585-32-1; 1 R_1 = H, R_2 = D, 87115-15-9; **2**, 76179-25-4; **4a**, 124225-39-4; **4b**, 124225-40-7; **5a**, 87115-22-8; **5b**, 87115-21-7; **6**, 124225-41-8; **7a**, 124225-42-9; **7b**, 124225-43-0; ethyl bromopyruvate, 70-23-5; trimethyl phosphite, 121-45-9.

(22) Gordon, A. J.; Ford, R. A. *The Chemist's Companion: A Handbook of Practical Data, Techniques and References*; John Wiley and Sons: New York, 1972.

(23) The conversion of **3** to **4a** and **4b** when carried out in refluxing diglyme (bp 162 °C) yields and 82:18 *Z*/*E* ratio. The separation of the *Z* and *E* isomers can also be effected via column chromatography using 100 g of *dry* silica gel/1 g of compound. The column is eluted at 100 mL/h with 100 mL of 5% EtOAc/heptanes (vol/vol), 200 mL of 10% EtOAc/heptanes, 300 mL of 15% EtOAc/heptanes, and finally 1 L of 20% EtOAc/heptanes until the product (R_f = 0.2 30% EtOAc/heptanes) was collected in >95% optical purity.

Stereochemistry in a Medium-Sized Ring. Highly Diastereoselective N-Oxidation of a Substituted 3-Benzazonine. X-ray Crystal Structure of an Unusual Complex between an Amine *N*-Oxide and Saccharin

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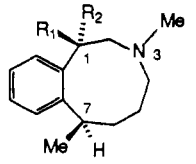
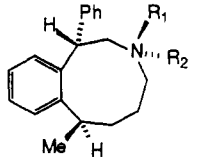
Medium-sized cyclic compounds often adopt a wide range of low-energy conformations, which can render the control of reaction stereochemistry unpredictable or difficult.[1-4] However, with the introduction of sp^2 atoms into the ring, certain conformations may be significantly differentiated, so that impressive diastereoselection between remote sites (e.g., 1,3 and 1,4) can be achieved.[1-3] Both Still[1] and Vedejs[2] have drawn attention to local conformational effects as a source of effective stereocontrol in such molecules.

Our interest in this area stems from our work with hexahydro-1-phenyl-3-benzazonine derivatives.[3] An important problem in this earlier paper was the stereochemical assignment of *cis*- and *trans*-**1**, which was predicated





trans-**1** R_1 = H, R_2 = Ph

cis-**1** R_1 = Ph, R_2 = H

2 R_1 = Me, R_2 = O

3 R_1 = O, R_2 = Me

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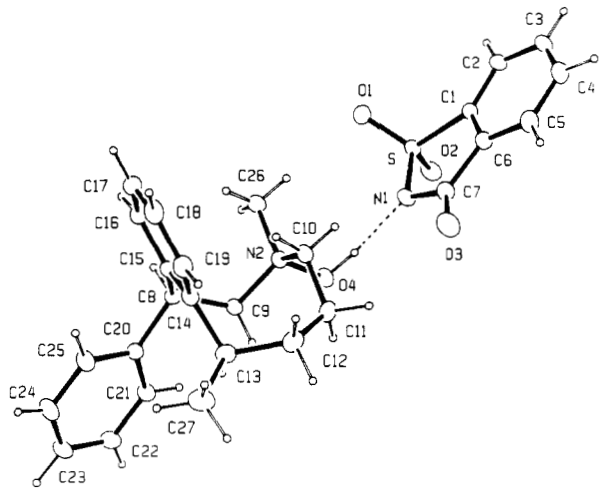

Figure 1. Molecular structure of **2**·saccharin showing the crystallographic numbering scheme and the hydrogen bond involving N1 and the hydrogen atom on O4.

on ^{1}H NMR spectral data.[3] To corroborate this critical assignment, we sought a single-crystal X-ray analysis on a salt of one of these isomers. However, the preparation of adequate crystals of the perchlorate[3] of *trans*-**1** or the fumarate[3] of *cis*-**1** could not be fulfilled, and other salts involving *trans*-**1** and 15 diverse acids were not crystalline. Ultimately, we obtained a suitable saccharin salt, X-ray analysis of which revealed, surprisingly, a complex between an *N*-oxide of *trans*-**1** (i.e., **2**) and saccharin. While we were naturally gratified at winning this X-ray structure and the concomitant stereochemical assignment, we were curious about where the *N*-oxide came from and fascinated by the high stereoselectivity of the N-oxidation. These issues comprise the basis of this paper.

Results and Discussion

A 100-mg sample of *trans*-**1**·$HClO_4$ was partitioned between aqueous NaOH and dry ethyl ether to release the free base. Treatment of the oily free base with saccharin immediately yielded a white crystalline substance (65% yield), which was recrystallized slowly to provide colorless prismatic needles. The expected 1:1 adduct (^{1}H NMR) was subjected to a single-crystal X-ray analysis, details of which are presented in the Experimental Section and the supplementary material.[5] Although the molecular structure shows the trans relationship between the substituents on positions 1 (C8) and 7 (C13), confirming our earlier assignment,[3] the compound turned out to be an *N*-oxide derivative of *trans*-**1** (Figure 1, crystallographic numbering used here). The oxygen atom O4, which is cis to the pendant phenyl group on crystallographic C8 and trans to the methyl group on C13, is protonated by the saccharin, such that the molecular complex actually represents a hydroxyammonium salt. The O4–H bond distance of 0.90 Å is quite consistent with this description. Additionally, the nitrogen of the saccharinate unit is hydrogen bonded

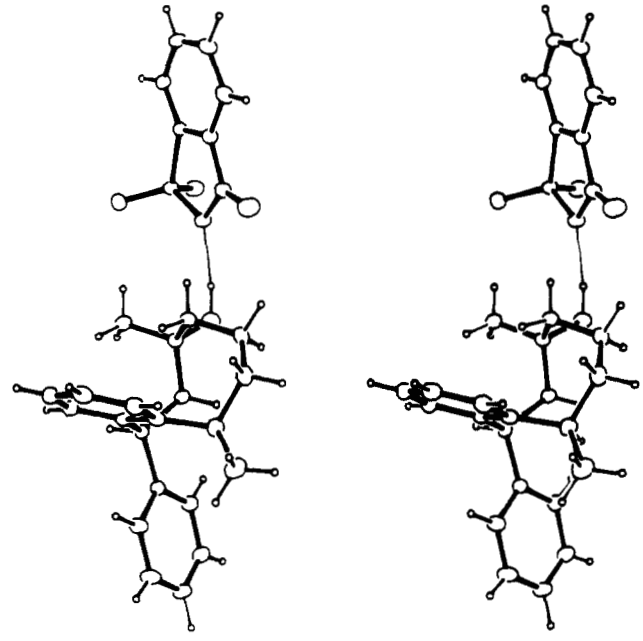

Figure 2. Stereoview of the molecular structure of **2**·saccharin.

to the hydrogen on O4 with a N1-H bond distance of 1.753 Å and a nearly linear N1···H–O4 bond angle of 174.4° (the N2–O4 bond distance is a reasonable 1.43 Å).[6] The conformation of the 9-membered ring of **2** in the solid state is illustrated by the stereopair in Figure 2. The ring adopts a boat–chair conformation with the atom sequences C9–C8–C15–C14–C13–C12 and C9–N2–C10–C11–C12 defining the boat and chair segments, respectively. This X-ray structure does not precisely mimic any of the four low-energy geometries calculated for amine **1**,[3] which account for 98.5% of the conformational distribution (see structures **4**–**7** in Figure 3), but it does come close to **4**, especially in the region C10–C11–C12–C13. One key difference between the X-ray structure and **4** pertains to the nitrogen end of the ring. The 7-methyl substituent (on C13) assumes an equatorial arrangement relative to the plane defined by atoms N2, C11, and C13, while the 1-phenyl substituent is axial relative to the C8–C11–C13 plane. Since N2 marks a conformational transition in **2**, it is difficult to specify the orientation of the N-substituents in terms of axial and equatorial.

Early on, we were surprised by this peculiar *N*-oxide salt for two reasons. First, we obviously did not suspect that an *N*-oxide could form so easily during basification of *trans*-**1**·$HClO_4$ and subsequent salt preparation; indeed, we had generated clean samples of *trans*-**1** before for NMR studies.[3] Second, we did not expect such a robust complex involving an amine *N*-oxide (weak base) and saccharin (fairly weak acid). However, there is some literature precedent for such complexes.[7,8] Etter and Baures[7] recently reported crystalline complexes between triphenylphosphine oxide and various primary and secondary amides, including saccharin.[7] They indicated that these $Ph_3P{=}O$ complexes rely on a strong hydrogen bond that imparts partial ionic character to the crystal, as seen for our complex in the solid state. Charpin et al.[8] described

(1) (a) Still, W. C.; Galynker, I. *Tetrahedron* **1981**, *37*, 3981. (b) Still, W. C.; MacPherson, L. J.; Harada, T.; Callahan, J. F.; Rheingold, A. L. *Ibid.* **1984**, *40*, 2275.

(2) Vedejs, E.; Dent, W. H., III; Gapinski, D. M.; McClure, C. K. *J. Am. Chem. Soc.* **1987**, *109*, 5437.

(3) Maryanoff, B. E.; Almond, H. R., Jr. *J. Org. Chem.* **1986**, *51*, 3295.

(4) Anet, F. A. L.; Krane, J. *Isr. J. Chem.* **1980**, *20*, 72.

(5) See paragraph at the end of this paper regarding supplementary material.

(6) For an X-ray structure determination on saccharin itself, see: Okaya, Y. *Acta Crystallogr., Sect. B* **1969**, *25*, 2257. The crystal structure showed a dimer formed by a N–H···O hydrogen bond between the imide nitrogen and the keto oxygen atoms.

(7) Etter, M. C.; Baures, P. W. *J. Am. Chem. Soc.* **1988**, *110*, 639.

(8) Charpin, P.; Dunach, E.; Kagan, H. B.; Theobald, F. R. *Tetrahedron Lett.* **1986**, *27*, 2989.

a stable crystalline 1:1 molecular complex between a chiral sulfoxide and a chiral secondary amide. As far as we know, complexes between amine *N*-oxides and saccharin have rarely been observed.[9]

The formation of **2** is probably connected to the use of ethyl ether in the basification of *trans*-**1**·$HClO_4$. On repeating this process with ethyl acetate or dichloromethane as the organic solvent, only the anticipated *trans*-**1** was obtained. We presume that a sufficient quantity of peroxides was present in the anhydrous ether (used in large excess) to convert almost all of the amine to the *N*-oxide.[10] This accidental oxidation was highly stereoselective since there was no evidence for the corresponding *N*-oxide diastereomer, **3**. Given this remarkable stereocontrol with a medium-sized ring, we examined the N-oxidation under more carefully controlled conditions.

A sample of *trans*-**1**, from basification of the perchlorate salt with ethyl acetate as solvent, was cleanly oxidized with *m*-chloroperbenzoic acid. ^1H NMR and FAB MS data indicated that the product was a mixture of **2** and **3** in ratio of ca. 92:8, although only **2** could be fully characterized by the ^1H NMR data. In the accidental oxidation above, **3** may have been formed to a very minor extent and then eliminated in the isolation process.

To rationalize this high stereoselectivity, we might consider ring conformations of *trans*-**1** and the approach of oxidant to the nitrogen lone pair. According to our prior report,[3] *trans*-**1** is populated mainly by two conformers, **4** (68%) and **5** (20.5%), while only two additional conformers, **6** (8%) and **7** (2%), exceed a level of 1%. The *N*-methyl in **4** is positioned exo and the lone pair is endo (1*S*,3*R*,7*R* configuration); thus, attack at nitrogen with retention would have to occur from the endo direction to generate minor diastereomer **3**. As this approach is sterically hindered, particularly by the fused benzene ring (distance of 2.6–2.8 Å), it should be unfavorable. The nitrogen lone pair in **5** is also endocyclic (1*R*,3*S*,7*S* configuration), and attack by the oxidant with retention would also produce the wrong isomer, **3**. Insofar as this avenue is hindered by transannular interaction with the ring methylene at position 6 (distances of 2.5 and 2.7 Å), it should be unfavorable as well. Production of the observed major product, **2**, from conformers **4** or **5** obviously requires inversion at nitrogen, to give significantly less stable conformations, such as **6** and **7** (1*S*,3*S*,7*R* configuration).[3] However, the nitrogen lone pair is in a hindered endocyclic orientation in these latter structures, too (distances of 2.5/2.6 Å in **6** and 2.4/3.3 Å in **7**). If we accept the force field calculations as being reasonable and the difficulty of endocyclic oxidation, then it is necessary to suggest that the high stereoselectivity stems from attack on a very minor conformation of **1** that possesses an exocyclic nitrogen lone pair (although very minor conformer **7**, being the least congested, may exhibit some competitive reactivity). This type of reactivity pattern exemplifies the well-known Curtin–Hammett principle.[11]

Experimental Section

General Procedures. Melting points are corrected. ^1H NMR spectra were recorded at 360 MHz on a Bruker AM-360WB instrument in $CDCl_3$ with Me_4Si as an internal standard, unless indicated otherwise. NMR proton assignments and coupling constants for **2** were derived with the aid of 2D COSY and homonuclear decoupling experiments. Fast-atom bombardment (FAB) mass spectral data were obtained on a VG 7070E spectrometer. TLC analysis was performed on 250-μm silica gel plates with visualization by UV fluorescence and iodine staining. The structures in Figure 3 were generated by using the SYBYL molecular modeling program (Tripos Associates, Inc., St. Louis, MO, version 5.1).

[1α,3α,7β]-2,3,4,5,6,7-Hexahydro-3,7-dimethyl-1-phenyl-1*H*-3-benzazonine *N*-Oxide (2), Compound with 1,2-Benzisothiazol-3-(2*H*)-one, 1,1-Dioxide (Saccharin). A sample of *trans*-**1**·$HClO_4$ (100 mg) was partitioned between 3 N sodium hydroxide (2 mL) and anhydrous ethyl ether (25 mL), with stirring for about 15 min to dissipate the solid. The ethereal extract was dried (Na_2SO_4) and concentrated in vacuo. The nearly colorless oil was dissolved in ethyl acetate (8 mL) and treated with a solution of saccharin (45 mg) in a small amount of warm ethyl acetate containing a drop of methanol. After addition of 2 mL of hexane, crystals began to separate. The mixture was cooled to 0 °C and filtered to give 95 mg (65%) of white powder. This material was recrystallized slowly from ethyl acetate/methanol (1:1, 3 mL) to yield 32 mg of bright colorless prismatic needles, mp 190–195 °C (turned red and intumesced), homogeneous by TLC with 1:1 chloroform/95% ethanol (R_f = 0.22); ^1H NMR δ 1.21 (d, 3, CMe, J = 6.7 Hz), 1.57–1.72 (m, 1, H6), 1.84–1.94 (m, 1, H6, ^2J = 14.2 Hz), 2.05–2.18 (m, 1, H5), 2.32–2.46 (m, 1, H5), 2.91–3.02 (m, 1, H4?), 3.61–3.73 (m, 4, s for NMe at δ 3.69), 2.74–2.83 (m, 1, H7, splitting due to Me is evident), 4.60–4.80 (m, 2, 2 H2 or H1 and H2), 4.85–4.92 (m, 1, H2 or H1), 7.13–7.35 (m, 7, Ar H in **2**), 7.43–7.50 (m, 2, Ar H in **2**), 7.57–7.65 (m, 2, saccharin), 7.77–7.84 (m, 2, saccharin); FAB MS, m/z 296 (M + H, 100%), 280 (loss of O, 35%).

The starting amine, *trans*-**1**, also made a fine crystalline salt with saccharin: colorless prisms from ethyl acetate/hexane, mp 148–151 °C; FAB MS, m/z 280 (M + H); ^1H NMR δ 1.12 (m, 3, Me), 1.5–1.7 (br m, 2), 1.7–1.9 (m, 1), 2.1–3.3 (m, 3), 2.86 (s, 3, NMe), 3.00 (m, 1), 3.1–3.2 (m, 1), 4.09 (dd, 1), 4.40 (m, 1), 4.6–4.7 (m, 1), 7.0–7.5 (m, 9), 7.60 (m, 2), 7.80 (m, 2); the aliphatic resonances in this spectrum were rather broad and ill-defined.

[1α,3α,7β]-2,3,4,5,6,7-Hexahydro-3,7-dimethyl-1-phenyl-1*H*-3-benzazonine *N*-Oxide (2) from MCPBA Oxidation of *trans*-1. A sample of *trans*-**1**·$HClO_4$ (20 mg) was partitioned between ethyl acetate and 1 N NaOH. The organic extract was dried (Na_2SO_4) and treated with 15 mg of MCPBA (85% assay). After 24 h, 10% aqueous Na_2CO_3 was added. The organic layer was separated, rinsed with brine, dried (Na_2SO_4), and concentrated to dryness under a stream of argon, then in vacuo, to furnish 11 mg (70%) of colorless semisolid. The product was homogeneous by TLC and gave a proper FAB MS. ^1H NMR showed one major diastereomer, **2**, and peaks attributable to the minor diastereomer, **3**. Comparison of the 7-Me and NMe in **2** and **3** gave a ratio of ca. 92:8. ^1H NMR data for **2**: δ 1.13 (d, Me, J = 6.8 Hz), 1.59 (dddd, H5a, ^2J = 14.1 Hz, ^3J(5a,6a) = 14.0 Hz, ^3J(4a,5a) = 11.6 Hz, ^3J(4e,5a) = 5.3 Hz), 1.82 (dddd, H5e, ^2J = 14.2 Hz, ^3J = 2.3, 2.3, 5.1 Hz), 1.95 (m, H6e), 2.47 (m, H6a), 2.68 (ddd, H7e, ^2J = 12.8 Hz, ^3J = 1.7, 5.8 Hz), 2.94 (ddq, H4a, ^3J(4a,5e) = ca. 2 Hz, ^3J(4a,5a) = 11.5 Hz, ^3J(4a,Me) = 6.8 Hz), 3.03 (ddd, H7a, ^2J = ca. 12 Hz, ^3J = ca. 12, ca. 1 Hz), 3.17 (s, NMe), 4.05 (dd, H3a, ^3J(2a,3a) = 13.0 Hz, ^3J(2e,3a) = 5.1 Hz), 4.45 (dd, H2a, J = 13, 13 Hz), 4.52 (dd, H2e, J = 13, 5.2 Hz), 7.0–7.4 (m, Ar). ^1H NMR data for **3**: δ 0.89 (d, Me), 2.56 (s, NMe); only these sharp signals could be assigned unambiguously to **3** because of its relatively low concentration.

Single-Crystal X-ray Analysis of 2·Saccharin. Crystals of $C_{27}H_{30}N_2O_4S$ (mw 478.61) are triclinic (space group $P\bar{1}$) with

(9) An extensive search of *Chemical Abstracts* revealed only one saccharin complex of this type. An adduct between β-narcotine *N*-oxide (an isoquinoline alkaloid structure) and saccharin was reported in a Japanese patent: *Chem. Abstr.* **1964**, *52*, P5312h. Amine oxides form salts with various strong and moderate acids, and a recent paper discussed complexes between an *N*-oxide and a phenol: Toda, F.; Mori, K.; Stein, Z.; Goldberg, I. *Tetrahedron Lett.* **1989**, *30*, 1841.

(10) (a) A small amount (ca. 10%) of unoxidized *trans*-**1** was found in the mother liquor from the isolation of **2**·saccharin. (b) After obtaining the X-ray result, we no longer had any original ether to evaluate the peroxide level. However, we subsequently compared the basification of *trans*-**1**·$HClO_4$ with ether that was peroxide-free and with ether that contained ca. 30 mg/L of peroxides, as assayed by Quantofix peroxide test strips. *N*-Oxide **2** was found only for the *latter* case in the residue from evaporation of the ether solvent (about 20% conversion); for either case, the ethereal extract before evaporation showed virtually no *N*-oxide.

(11) Eliel, E. L.; Allinger, N. L.; Angyal, S. J.; Morrison, G. A. *Conformational Analysis*; Wiley-Interscience: New York, 1965, p 28.

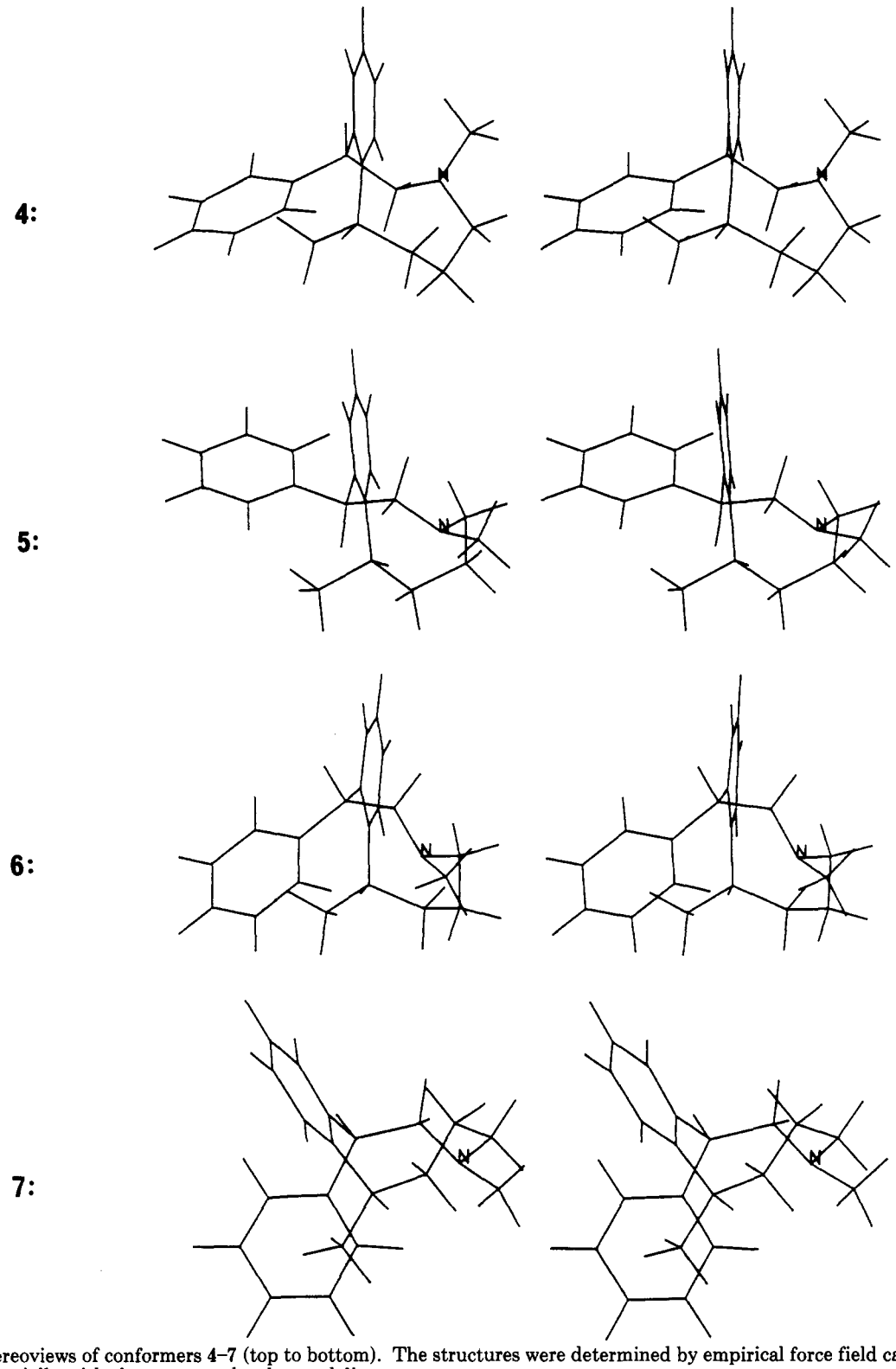

Figure 3. Stereoviews of conformers 4–7 (top to bottom). The structures were determined by empirical force field calculations[3] and generated pictorially with the SYBYL molecular modeling system.

a = 7.670 (3) Å, b = 12.516 (3) Å, c = 14.525 (4) Å, α = 64.28(2)°, β = 73.10 (2)°, γ = 82.38 (2)°, V = 1201.9 (10) Å^3, and d_{calcd} = 1.323 g cm^{-1} for Z = 2. The intensity data were collected from a single crystal on an Enraf-Nonius CAD4 diffractometer with the $\omega/2\theta$ scan method at 293 K (θ_{max} = 25°, ω-scan width = 0.80 + 0.35 tan θ, μ = 1.628 cm^{-1}) by using Mo Kα radiation (λ = 0.71073 Å). The programs employed were part of the Enraf-Nonius Structure Determination Package, as revised in 1982, implemented on a PDP 11/34 computer. The data were corrected for Lorentz and polarization factors but not for absorption. Of the 3867 total reflections, 2819 measuring greater than $3\sigma(I)$ were used. The structure was solved by direct methods and refined by full-matrix least-squares calculations. The hydrogen atoms were refined isotropically with B = 4.0 Å^2. The final discrepancy factors were R = 0.038 and $R_w = (\sum\Delta^2/\sum wF_o^2)^{1/2}$ = 0.052; the final difference map had no peaks greater than 0.26 e Å^{-3}.

Acknowledgment. We thank Dr. Harold Almond, Jr. for helpful discussions on 9-membered ring conformations.

Registry No. *trans*-1·HClO$_4$, 124439-12-9; **2**, 124342-87-6; **2**·saccharin, 124378-95-6; **3**, 124378-96-7; saccharin, 81-07-2.

Supplementary Material Available: Tables of bond distances, bond angles, and positional and thermal parameters for hydrogen and non-hydrogen atoms (9 pages). Ordering information is given on any current masthead page.

Isolation and Unusual Stability of a New Macrocyclic Polyamine Containing a Phthalimidine

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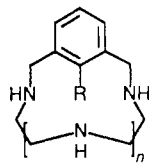
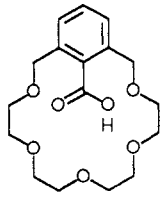
The host properties of macrocyclic polyamines containing a 2-hydroxy-1,3-xylyl unit as part of the large ring (**1** and **2**) are of great interest.[1] Effective uptake of alkaline-earth metal ions by them in MeOH has been achieved with the 1:1 complexation constants being in the order of $Mg^{2+} > Ca^{2+} > Sr^{2+} > Ba^{2+}$. Moreover, the simultaneous dissociation of the phenolic H^+ has allowed for the facile determination of complexation constants.



1: n = 2, R = OH
2: n = 3, R = OH
3: n = 3, R = COOH



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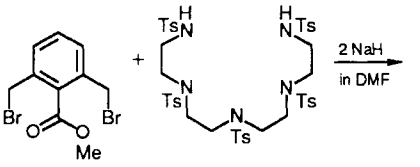
In order to develop further the chemistry of host polyamines, we have attempted to synthesize macrocycle **3**. This putative new compound **3** would be of interest in that its benzyl nitrogens could be close enough to the carboxyl substituent so that the lone pair of each benzyl nitrogen points toward the carbonyl carbon along the axis of its π system. Such overlap could conceivably lead to some unusual properties for the carbonyl group in **3**. In the polyether counterpart **4**,[2] for instance, the distances of the O···C=O bond were observed to be shorter than the usual van der Waals contacts, suggesting the presence of attractive dipole–dipole interactions.[3]

A new macrocycle (**6**) was prepared from dibromide **5** and tetraethylenepentamine pentatosylate in order to explore the above possibilities. Compound **6** was then heated at reflux in 48% HBr–acetic acid solution over a period of 48 h to complete the detosylation. Usual workup by anion exchange chromatography and recrystallization from acetonitrile then afforded a product as prismatic crystals, which on the basis of the reaction sequence was expected to be **3**. Elemental analysis, ^1H and ^{13}C NMR, IR, and UV spectra, and other physicochemical data for this product, however, did not fit to the anticipated structure **3**. This left some doubts about the structural assignment. The structure of this material was therefore



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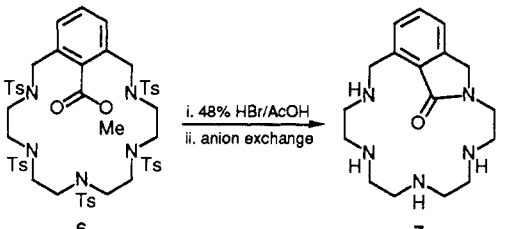
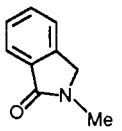


6 **7**



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determined by X-ray diffraction analysis and on this basis assigned unequivocally as compound **7** (Figure 1).

In addition to allowing for the structural assignment, the X-ray structure provides interesting details about the macrocyclic conformation, where the planar phthalimidine ring stands almost vertically to create a shielded cavity for guest ions.

The protonation constants (pK_a) were determined by pH (see Figure 2) to be 9.9, 9.2, 5.9, and 2.2 at I = 0.1 M ($NaClO_4$), 25 °C, indicating feasible accommodation of two protons into the macrocyclic cavity. The UV spectral absorptions (220–280 nm) of the phthalimidine are substantially increased in intensity in macrocycle **7**, as compared to *N*-methylphthalimidine itself (structure **8**). Moreover, in **7**, successive addition of protons affects the UV absorptions at 240–280 nm, whereas the UV absorption of **8**, as expected, is not subject to such proton dependence.

A similar significant UV absorption change was observed upon Zn^{2+} and Cu^{2+} uptake (up to 1:1 molar ratio). The pH–titration method has established 1:1 complexation with Zn^{2+} and Cu^{2+} (Figure 2). From the titration curve the modes of complexation of Cu^{2+} and Zn^{2+} are suggested to be as shown in Scheme I.

Detailed computational analysis of the experimental curves has allowed the values of the complexation constants to be determined as log K_{CuHL} = 12.2 (K_{CuHL} = $[Cu^{II}HL]/[Cu^{II}][HL]$), log K_{CuL} = 15.3 (K_{CuL} = $K_{CuHL} \times K'_{CuL}/K_1$, where $K' = [Cu^{II}L] \times a_{H^+}/[Cu^{II}HL]$), and log K_{ZnL} = 8.1 ($K_{ZnL} = [Zn^{II}L]/[Zn^{II}][L]$).[4] The considerably smaller K values observed here relative to those for unsubstituted N_4 macrocyclic ligands[5] may indicate that the stretched N_4 ring conformation present in **7** is unfavorable for metal incorporation (due to lack of flexibility).

The amide bond in macrocyclic **7** strongly resists hydrolysis in acid (e.g., refluxing 6 N HCl) and use of Zn^{2+} or Cu^{2+} ions (which were tried in an effort to activate the

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(4) The titration data of **7** in the presence of each metal ion (see dots on lines (b) and (c) in Figure 2) were treated by the Schwarzenbach method for the 1:1 complexation [Schwarzenbach, G. *Helv. Chim. Acta* **1950**, *33*, 947]. The metal hydrolysis was taken into account, where K_{OH} (= $[M(OH)^+]/([M^{2+}]a_{OH^-})$) values are 4.6×10^6 for Cu^{II} and 1.1×10^5 for Zn^{II} [Iitaka, Y.; Koike, T.; Kimura, E. *Inorg. Chem.* **1986**, *25*, 402].
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