amino-3,4,5,6-tetranitrotoluene (2) as yellow crystals (0.42 g, mp 183–185 °C).

Pentanitrotoluene (5). Method A. 2-Amino-3,4,5,6-tetranitrotoluene (2) (0.35 g, 1.1 mmol) was dissolved in 96% sulfuric acid (12.5 mL) and 30% oleum (10 mL). The solution was cooled to 0 °C, and 88% hydrogen peroxide (1.7 mL) was added dropwise with stirring. The solution was allowed to warm to ambient temperature and was stirred overnight. The reaction mixture was extracted with dichloromethane (4 × 50 mL); the extract was dried over anhydrous magnesium sulfate and was evaporated to give a pale yellow solid (0.30 g, 78%). Recrystallization from chloroform gave pale yellow crystals (0.24 g, mp 224–235 °C) (IR (KBr) 1550 cm^{-1} (NO_2); NMR (acetone-d_6) 2.71 (s, 3, CH_3)) identified as pentanitrotoluene (5). Anal. Calcd for $C_7H_3N_5O_{10}$: C, 26.50; H, 0.95; N, 22.08. Found: C, 26.64; H, 0.92; N, 21.97).

Dissolution of 3-amino-2,4,5,6-tetranitrotoluene (3) in a 1:2 mixture of 96% sulfuric acid and 20% oleum and oxidation using 98% hydrogen peroxide gave 5 in 79% yield, while oxidation of 4-amino-2,3,5,6-tetranitrotoluene (4) by the same method also yielded 5 in 82% yield.

3,5-Diamino-2,4,6-trinitrotoluene (30). Method A. Pentanitrotoluene (8) (0.20 g, 0.63 mmol) was dissolved in tetrahydrofuran (10 mL); a 0.4 N solution of ammonia in dioxane (30 mL) was added with an immediate color change from yellow to orange. After 10 min at ambient temperature, the solution was evaporated to dryness. Chromatography (silica gel/chloroform) gave a yellow solid, which was recrystallized from chloroform to give orange needles (0.12 g, 74%, mp 222.5–224 °C) (IR (KBr) 3440 and 3320 (NH_2) and 1600 cm^{-1} (NO_2); NMR ($CDCl_3$) δ 8.30 (br s, 4, NH_2) and 2.40 (s, 3, $ArCH_3$)) identified as 3,5-diamino-2,4,6-trinitrotoluene (30).[15] Anal. Calcd for $C_7H_7N_5O_6$: C, 32.65; H, 2.73; N, 27.26. Found: C, 32.65; H, 2.71; N, 27.13.

3,5-Diamino-2,4,6-trinitrotoluene (30). Method B. 3-Amino-2,4,5,6-tetranitrotoluene (3) (0.109, 0.35 mmol) was dissolved in dioxane (5 mL); a 0.42 N solution of ammonia in dioxane was added with stirring. After 5 min, the reaction mixture was evaporated to dryness. The residue was dissolved in dichloromethane (25 mL) and was washed with water. Drying over anhydrous magnesium sulfate, evaporating, and recrystallization from chloroform/carbon tetrachloride gave orange crystals (0.06 g, 67%; mp 223–225 °C) identified as 3,5-diamino-2,4,6-trinitrotoluene (30).

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Registry No. 2, 84432-57-5; 3, 84432-56-4; 4, 84432-53-1; 5, 73334-00-6; 6, 21985-87-5; 8, 3058-38-6; 10, 35572-78-2; 11, 65321-68-8; 12, 19406-51-0; 15, 84432-52-0; 17, 84432-54-2; 19, 84432-55-3; 21, 103025-34-9; 22, 91125-10-9; 23, 103025-35-0; 24, 3484-26-2; 25, 103025-36-1; 26, 103025-37-2; 27, 91125-09-6; 28, 103025-38-3; 29, 103025-39-4; 30, 73334-04-0; acetyl chloride, 75-36-5; formaldehyde, 50-00-0.

(15) Joshi, S. S.; Gupta, S. P. *J. Indian Chem. Soc.* **1959**, *36*, 329.

Alkoxyoxaziridines. Stereochemical Aspects of Imidate Oxidation, an Asymmetric Synthesis, and Unusually Facile *E–Z* Isomerizations[1]

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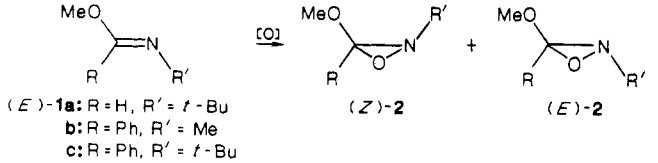
The synthesis of new, mechanistically useful 3-methoxy-3-phenyloxaziridines was accomplished by oxidation of imidate esters with *m*-chloroperbenzoic acid. Unlike previously known imidates, methyl *N-tert*-butylbenzimidate undergoes rapid *E–Z* isomerization at room temperature. Oxidation at ca. −10 °C gave 2-*tert*-butyl-3-methoxy-3-phenyloxaziridine [(*E*)-2c] in 22% yield as a 40:60 mixture of *E/Z* isomers in a kinetically controlled process. These and other stereochemical results suggest that oxidation occurs to some extent via a Baeyer–Villiger-type mechanism. Oxidation of methyl *N-tert*-butylformimidate with peroxycamphoric acid produced an excess of the *l* enantiomer of (*E*)-2-*tert*-butyl-3-methoxyoxaziridine. While most oxaziridines undergo slow N inversion, an unusually fast *E–Z* isomerization was observed for (*E*)-2c with activation parameters and an inverse solvent effect which suggested a zwitterion intermediate.

After the classic papers by Emmons,[2] investigations of oxaziridine chemistry entered a relatively dormant period,[3] but interest in this reactive ring system has recently been renewed with mechanistic,[4] reactivity,[5] and stereochemical studies.[6] In addition, two new classes of oxaziridines have been synthesized, one with a highly electron-withdrawing

Scheme I



(1) Work supported in part by the Naval Surface Weapons Center (White Oak, MD).

(2) (a) Emmons, W. D. *J. Am. Chem. Soc.* **1956**, *78*, 6208. (b) Emmons, W. D. *Ibid.* **1957**, *79*, 5739. (c) Emmons, W. D. *Ibid.* **1957**, *79*, 6522.

(3) For reviews, see: (a) Emmons, W. D. In *Heterocyclic Compounds with Three- and Four-Membered Rings*; Weissberger, A., Ed.; Wiley: New York, 1964; Part 1, p 624. (b) Schmitz, E. *Adv. Heterocycl. Chem.* **1963**, *2*, 83; **1979**, *24*, 63.

(4) (a) Madan, V.; Clapp, L. B. *J. Am. Chem. Soc.* **1969**, *91*, 6078. (b) Madan, V.; Clapp, L. B. *Ibid.* **1970**, *92*, 4902. (c) Ogata, Y.; Sawake, Y. *Ibid.* **1973**, *95*, 4687. (d) Ogata, Y.; Sawake, Y. *Ibid.* **1973**, *95*, 4692. (e) Butler, A. R.; White, J. G.; Challis, B. C.; Lobo, A. M. *J. Chem. Soc., Perkin Trans 2* **1979**, 1039 and references therein. (f) Rastetter, W. H.; Wagner, W. R.; Findeis, M. A. *J. Org. Chem.* **1982**, *47*, 419. (g) Oliveros, E.; Riviere, M.; Malrieu, J. P.; Teichteil, Ch. *J. Am. Chem. Soc.* **1979**, *101*, 318. (h) Ogata, Y.; Takagi, K.; Mizuno, K. *J. Org. Chem.* **1982**, *47*, 3684.

(5) (a) Hata, Y.; Watanabe, M. *J. Am. Chem. Soc.* **1979**, *101*, 6671. (b) Hata, Y.; Watanabe, M. *J. Org. Chem.* **1981**, *46*, 610. (c) Nastasi, M.; Streith, J. In *Rearrangements in Ground and Excited States*; deMayo, P., Ed.; Academic: New York, 1980; p 445.

(6) (a) Bjorgo, J.; Boyd, D. R.; Campbell, R. M.; Thompson, N. J.; Jennings, W. B. *J. Chem. Soc., Perkin Trans. 2* **1976**, 606 and references therein. (b) Boyd, D. R.; Neill, D. C.; Watson, C. G.; Jennings, W. B. *Ibid.* **1975**, 1813. (c) Bucciarelli, M.; Forni, A.; Moretti, I.; Torre, G. *Ibid.* **1977**, 1339.

0022-3263/86/1951-3266$01.50/0

SO_2Ar group on nitrogen,[7] which is finding utility as an oxidizing agent,[8] and the other with an electron-donating alkoxy group on the ring carbon.[9]

Unlike the case for the 2-(arylsulfonyl)oxaziridines,[7b] the stereochemistry of peracid oxidation of imidate esters to give 3-alkoxyoxaziridines has not been investigated. Although cyclic cases had fixed *E* configurations of both imidate and oxaziridine,[9] the *E*–*Z* nature of reactants and products for acyclic cases has not been addressed.

This paper describes our extension of the method of Aue and Thomas[9] to prepare 3-phenyl-3-methoxyoxaziridines. The stereochemistry of such compounds could readily be determined and used to provide mechanistic insight into the oxidation step. In addition, the availability of 3-aryl systems will be useful for structure–reactivity studies. We also report the first asymmetric synthesis of an alkoxyoxaziridine, which likewise can have use in mechanistic studies, and the unusually facile *E*–*Z* isomerization of these oxaziridines.

Results and Discussion

The 3-methoxyoxaziridines were prepared by oxidation of corresponding methyl imidates by *m*-chloroperbenzoic acid according to Scheme I. As noted by other workers for oxaziridines without the methoxy group,[3,7b] an *N*-*tert*-butyl group stabilized the ring system compared to an *N*-methyl. Thus, while **2b** was unstable at room temperature and attempts to isolate it produced only methyl benzoate, **2c** was distillable in 22% yield and gave a satisfactory elemental analysis. Both oxaziridines showed the absence of C=N in the IR and gave NMR spectra in agreement with structures presented. The mass spectrum of **2c** showed a similar fragmentation pattern to that reported[9] for **2a** but with additional peaks expected for the phenyl group.

Preference for *E* Isomers. Different methods were used to prepare imidates: **1a** by alkylation of the amide with trimethyloxonium tetrafluoroborate[9b] or methyl triflate; **1b** by methanolysis of the imino chloride;[10a] **1c** by treatment of the amide with methyl fluorosulfonate.[10b] Imidates **1a** and **1b** existed as single isomers in CD_2Cl_2 on the basis of singlets in their NMR spectra. The spectrum of **1a** did not change as the temperature was lowered to −40 °C, and the coalescence temperature for *E*–*Z* isomerization of **1b** has been reported to be 94 °C in phenol/nitrobenzene.[11] Both were assigned the *E* configuration on the basis of NOE experiments.[12]

These imidate assignments are consistent with the literature data.[13a] In the case of **1a** ab initio MO calculations showed that the *E* antiperiplanar isomer of the parent compound, formimidic acid, was more stable than *Z* isomers by at least 3.77 kcal/mol[13b] and homoallylic long-range coupling constants of 1, R = R′ = CH_3, and 1,R = CH_3, R′ = C_2H_5, showed that these derivatives existed exclusively as *E* isomers in carbon tetrachloride.[13c] For **1b** dipole moment measurements compared to cyclic imidates necessarily of the *E* configuration showed that **1b** exists as the *E* isomer in benzene at 25 °C.[14]

Nonbonded interactions could conceivably force **1c** into a *Z* configuration, since the *Z* isomer can become more favored when steric factors become important. For example, 1 with R = *t*-Bu and R′ = CH_3 consists of an 87:13 *E*/*Z* mixture.[13c] Indeed, the 300-MHz NMR of the previously unreported **1c** showed broad singlets at 1.12 (*t*-Bu) and 3.58 ppm (CH_3O) at ca. 27 °C in CD_2Cl_2. At −67 °C these are resolved into peaks corresponding to *E* (1.04 and 3.62 ppm) and *Z* (1.34 and 3.52 ppm) isomers, where assignments are based on analogous chemical shifts[11] and NOE experiments.[12] At −10 °C where oxidation to **2** was carried out, the *E*/*Z* ratio was 62:38. This is to our knowledge the first case of an imidate that undergoes rapid configuration isomerization at room temperature.

The stereochemistry of oxaziridines with 3-phenyl groups can be determined from chemical shifts of *N*-alkyl protons. Earlier work on oxaziridines with stereochemistry unambigously determined by X-ray structures[6a,15] or NOE experiments[16a] showed that protons of *N*-methyl, *N*-isopropyl, or *N*-*tert*-butyl groups cis to a 3-phenyl group were shifted abnormally upfield, presumably due to such protons lying in the benzene shielding cone.

Oxidation of **1a** gave **2a** as only one isomer. The absence of a second isomer precluded assignment of configuration based on the chemical shift of the methine hydrogen.[7b] However, it seems reasonable that **2a** is the *E* isomer on the basis of the above results and the results of Boyd et al. for various *N*-*tert*-butyloxaziridines.[16b] Oxidation of **1b** gave a mixture with *N*-methyl absorptions at 2.87 ppm and one upfield at 2.36 ppm, corresponding to a 62:38 mixture of *E*/*Z* isomers which were configurationally stable under the reaction conditions.

Oxidation of **1c** at ca. −10 °C gave an oxaziridine mixture showing two *tert*-butyl singlets, one at 1.25 ppm and one upfield at 0.87 ppm, corresponding to *Z* and *E* isomers, respectively. From integrations, this consisted of a 40:60 mixture of *E*/*Z* isomers. The reaction must be kinetically controlled, since the isomer distribution inverted with time and reached an equilibrium value of 76:24 *E*/*Z* at 20 °C in methylene chloride. On cooling a vacuum-distilled sample to −8 °C, pure (*E*)-**2** crystallized.

One important factor favoring the *E* configuration of imidates is the favorable dipole–dipole orientation of the *E* antiperiplanar conformer shown in **3**.[13a,c,14a] This factor in **4** may also contribute to the preference for *E* oxaziridines. Based on similar results for oxaziridines *without* the 3-methoxy group,[6b] another important factor may be

(7) (a) Davis, F. A.; Nadir, U. K.; Kluger, E. W. *J. Chem. Soc., Chem. Commun.* **1977**, 25. (b) Davis, F. A.; Lamendola, J., Jr.; Nadir, V.; Kluger, E. W.; Sedergran, T. C.; Panunto, T. W.; Billmers, R.; Jenkins, R., Jr.; Turchi, I. J.; Watson, W. H.; Chen, J. S.; Kimura, M. *J. Am. Chem. Soc.* **1980**, *102*, 2000. (c) Davis, F. A.; Stringer, O. D. *J. Org. Chem.* **1982**, *47*, 1774.

(8) (a) Davis, F. A.; Jenkins, R., Jr.; Rizvi, S. Q. A.; Panunto, T. W. *J. Chem. Soc., Chem. Commun.* **1979**, 600. (b) Davis, F. A.; Abdul-Malik, N. F.; Awad, S. B.; Harakal, M. E. *Tetrahedron Lett.* **1981**, *22*, 917. (c) Boschelli, D.; Smith, A. B., III; Stringer, O. D.; Jenkins, R. H., Jr.; Davis, F. A. *Tetrahedron Lett.* **1981**, *22*, 4385. (d) Davis, F. A.; Jenkins, R. H., Jr.; Awad, S. B.; Stringer, O. D.; Watson, W. H.; Galloy, J. *J. Am. Chem. Soc.* **1982**, *104*, 5412. (e) Davis, F. A.; Harakal, M. E.; Awad, S. B. *J. Am. Chem. Soc.* **1983**, *105*, 3123. (f) Davis, F. A.; Billmers, J. M. *J. Org. Chem.* **1983**, *48*, 2672. (g) Davis, F. A.; Stringer, O. D.; Billmers, J. M. *Tetrahedron Lett.* **1983**, *24*, 1213.

(9) (a) Aue, D. H.; Thomas, D. *Tetrahedron Lett.* **1973**, 1807. (b) Aue, D. H.; Thomas, D. *J. Org. Chem.* **1974**, *39*, 3855.

(10) (a) Challis, B. C.; Frenkel, A. D. *J. Chem. Soc., Perkin Trans. 2* **1978**, 192. (b) Beak, P.; Lee, J. K.; McKinnie, B. G. *J. Org. Chem.* **1978**, *43*, 1367.

(11) Walter, W.; Meese, C. O. *Chem. Ber.* **1977**, *110*, 2463.

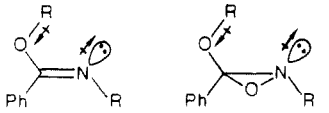
(12) Gallis, D. E.; Crist, D. R., submitted for publication.

(13) (a) For analogous systems, see: Fodor, G.; Phillips, B. A. *The Chemistry of Amidines and Imidates*; Patai, S., Ed.; Wiley: New York, 1975; pp 132–135. Hafelinger, G. *The Chemistry of Amidines and Imidates*; Patai, S., Ed.; Wiley: New York, 1975; pp 61, 84. (b) Radom, L.; Hehre, W. J.; Pople, J. A. *J. Am. Chem. Soc.* **1971**, *93*, 289. (c) Meese, C. O.; Walter, W.; Berger, M. *Ibid.* **1974**, *96*, 2259.

(14) Exner, O.; Schindler, O. *Helv. Chim. Acta* **1972**, *55*, 1921.

(15) (a) Boyd, D. R.; Jerina, D. M.; Cannon, J. F.; Daly, J.; Silverton, J. V. *J. Chem. Soc., Perkin Trans. 2* **1972**, 1137. (b) Boyd, D. R.; Jennings, W. B.; Watson, C. G.; Becker, E. D.; Bradley, R. B.; Jerina, D. M. *J. Am. Chem. Soc.* **1972**, *94*, 8501.

(16) (a) Boyd, D. R.; Jennings, W. B.; Spratt, R. *J. Chem. Soc., Chem. Commun.* **1970**, 745. (b) Boyd, D. R.; Waring, L. C.; Jennings, W. B. *J. Chem. Soc., Perkin Trans. 1* **1978**, 243 and references therein.



3 4

an unfavorable interaction between the nitrogen lone pair and the benzene π electrons in the Z isomer of **4**.

Mechanism of Oxidation. Two mechanisms for peracid oxidation of imines were suggested by Emmons based on his synthetic results,[2b] and both have been supported by more recent kinetic studies. One is a concerted process[4a,b] similar to epoxidation of alkenes and the other a two-step mechanism[4c,d] that is similar to the Baeyer–Villiger reaction and has been supported by an ab initio MO study.[17] While a concerted oxidation is possible for **1a**, a significant fraction of the reaction must proceed by a different pathway for **1b**, since an E/Z product mixture resulted from the E reactant. For **1c**, the situation is more complex due to significant E/Z isomerizations of reactant and product as shown in Scheme II.

For a mixture favoring the E imidate to give a kinetically controlled 40:60 mixture favoring the Z oxaziridine by a concerted mechanism, the relative values of rate constants must be $k_1, k_2 \gg k_3 > k_4$. It might be noted that if partial equilibration of E/Z products had occurred, kinetic control would be even more dramatic than apparent from the observed E/Z ratios.

Unfortunately, kinetic data are not available to test this mechanism.[18] However, it seems unlikely that k_3 is sufficiently greater than k_4 for the following reasons: (1) as indicated in Scheme II, models suggest planarity of the imine double bond with phenyl in (*Z*)-**1c** (but not in (*E*)-**1c** in which these groups are forced to be perpendicular due to the steric crowding of R′ and an ortho hydrogen); the Z isomer thus resembles *trans*-stilbene, which is oxidized *slower* than the less conjugated *cis*-stilbene,[19,6b] and (2) unfavorable dipole–dipole and nitrogen lone pair–phenyl orientations are partially developed in $Z^{\ddagger}$ so that it is not clear why $Z \rightarrow Z^{\ddagger}$ should have a significantly lower $\Delta G^{\ddagger}$ than $E \rightarrow E^{\ddagger}$.[20]

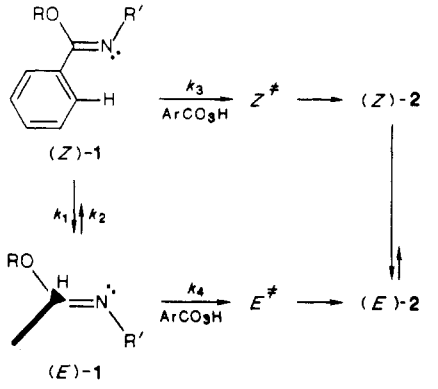
A two-step process shown in Scheme III is more consistent with results for **1b** and **1c**. The dipolar attractions in imidate (*E*)-**1** no longer exist in the Baeyer–Villiger adduct **5**. Hence, rotation around the C–N single bond to give **6** results in relief of steric interactions between the bulky phenyl and *N*-alkyl groups.

This effect would be more pronounced in the *tert*-butyl case, in agreement with the observed stereoselectivity. Nitrogen inversion in **6** followed by ring closure gives the observed kinetically controlled product (*Z*)-**2**.

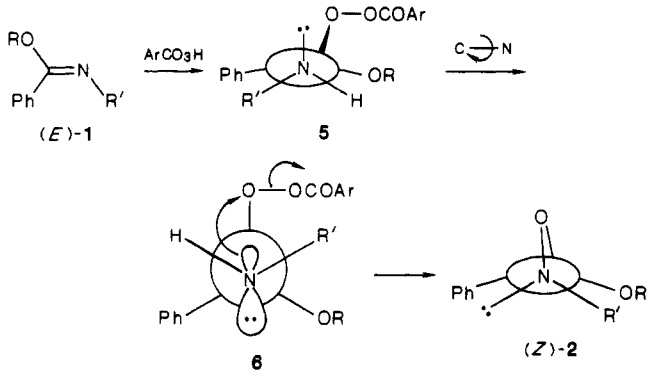
In support of this mechanism are stereochemical studies with other oxaziridines[6b] and formation of Baeyer–Villiger products in two cases,[7b,9b] one involving oxidation of a cyclic imidate under the same conditions as the present study.[9b]

Asymmetric Synthesis of 2a. Oxidation of imines with chiral oxidizing agents has been known for some time.[21] In view of the unusual dipole–dipole interaction in imidate esters, it was of interest to see if these methods could be extended to oxidation of this type of imine. It was found that oxidation of **1a** with optically active peroxycamphoric acid at 40 °C gave **2a** in 22% yield with $[\alpha]^{25}_{D}$ −3.3° (*c* 0.31, $CHCl_3$). Since the rotations of pure isomers are not known, the enantiomeric excess is also not known. Only one isomer was detected by NMR, and this was assumed to be the E isomer as discussed above.

Scheme II



Scheme III



***E–Z* Isomerization of Alkoxyoxaziridine 2c.** The relatively fast E–Z equilibration observed for **2c** at 21 °C is very unusual for oxaziridines that are configurationally stable at room temperature[20,21] and normally require elevated temperatures (where stability permits) for significant isomerization.[23] Consequently, a kinetics study was carried out, with results given in Table I where k_1 represents the $E \rightarrow Z$ process and k_2 the reverse. The temperature dependence of rate constants yielded enthalpies of activation (to ±2 kcal/mol) for **2c** in CCl_4 of 13 and 6 kcal/mol for $\Delta H_1^{\ddagger}$ and $\Delta H_2^{\ddagger}$, respectively, and entropies of activation (to ±7 eu) of −34 and −54 eu for $\Delta S_1^{\ddagger}$ and $\Delta S_2^{\ddagger}$, respectively.

Three observations can be made regarding these data. First, **2c** with $\Delta G^{\ddagger}$ of 22 kcal/mol for k_{obsd} at 294 K in CCl_4 isomerizes significantly faster than N-*tert*-butyladamantanespiro-3′-oxaziridine, the first oxaziridine to isomerize appreciably at ambient temperature,[24] with a $\Delta G^{\ddagger}$ of 24 kcal/mol (in tetrachloroethylene at 299 K). Second, the reaction goes faster in the more polar *o*-di-

(17) Azman, A.; Koller, J.; Plesnicar, B. *J. Am. Chem. Soc.* **1979**, *101*, 1107.

(18) For example, if it were known that isomerization of **1c** is fast relative to oxidation, the Curtin–Hammett principle would apply. It *is* probable, however, that acid catalysis of k_1 and k_2 is not important, since 90 h at 80 °C was required for equilibration of *C*-alkylbenzimidates in 100% H_2SO_4. See Moriarty et al. (Moriarty, R. M.; Yeh, C. L.; Ramey, K. C.; Whitehurst, P. W. *J. Am. Chem. Soc.* **1970**, *92*, 6360) but with assignment of configuration as the E isomers according to ref 13c.

(19) Lynch, R. B.; Pausacker, K. H. *J. Chem. Soc.* **1955**, 1525.

(20) In support of $k_3 > k_4$, however, it should be pointed out that the double bond in (*Z*)-**1** seems sterically more accessible due to possible ortho hydrogen interference in (*E*)-**1** (see Scheme II).

(21) (a) Boyd, D. R. *Tetrahedron Lett.* **1968**, 4561. (b) Boyd, D. R.; Graham, R. *J. Chem. Soc. C* **1969**, 2648. (c) Montanari, F.; Moretti, I.; Torre, G. *Chem. Commun.* **1968**, 1694. (d) Boyd, D. R.; Jerina, D. M.; Spratt, R. *J. Chem. Soc. C* **1969**, 2650.

(22) Mannschreck, A.; Linss, J.; Seitz, W. *Justus Liebigs Ann. Chem.* **1969**, *724*, 224.

(23) For review, see: (a) Lehn, J.-M. *Topics in Current Chemistry*; Springer-Verlag: Berlin, 1970: Vol. 15, p 312. (b) Lambert, J. B. In *Topics in Stereochemistry*; Allinger, N. L., Eliel, E. L., Eds.; Wiley-Interscience: New York, 1971; Vol. 6, p 19.

(24) Bjorgo, J.; Boyd, D. R. *J. Chem. Soc., Perkin Trans. 2* **1973**, 1575.

Table I. Rate Constants for E-Z Equilibration of 2c[a]

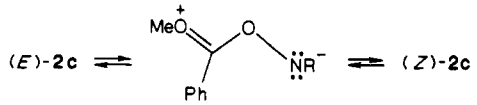
solv	T, °C	K_{eq}	10^4k_{obsd}, s^{-1}	10^4k_1, s^{-1}	10^4k_2, s^{-1}
CCl_4	20.6	0.161	4.58 ± 0.26	0.635	3.95
CCl_4	30.8	0.286	5.17 ± 0.13	1.15	4.02
CCl_4	39.7	0.330	10.5 ± 0.1	2.60	7.9
o-$C_6H_4Cl_2$	39.9	0.334	14.0 ± 1.3		

[a] Values of k_{obsd} from least-squares slope in ln ($[E] - [E]_\infty$) vs. t.

chlorobenzene solvent than in carbon tetrachloride, a solvent effect opposite to that for simple N inversion.[23a,25] Finally, $\Delta H^\ddagger$ values for **2c** are considerably lower than those of 24–34 kcal/mol found for other oxaziridines[23a,24,26] (e.g., 27.7 kcal/mol for the 3,3-diphenyl analogue of **2c**[26]). They are also much lower than the 32.4 kcal/mol calculated for the energy barrier to nitrogen inversion by SCF-LCAO methods.[27]

It thus appears that **2c** isomerizes by a mechanism different from simple N inversion which probably occurs for other oxaziridines, e.g., for 2-*tert*-butyl-3-methyl-3-(4-nitrophenyl)oxaziridine as shown by retention of configuration at the ring carbon during isomerization.[28]

A possible interpretation of the data is that isomerization proceeds via zwitterion **7** analogous to the case for aziridinedicarboxylic esters.[29] Unlike the ring oxygen whose lone pair orbitals are gauche to the breaking C–N bond, the methoxy oxygen lone pairs can be oriented antiperiplanar in a conformation favorable to participation in ring opening,[30] thereby leading to the low $\Delta H^\ddagger$ for **2c**. In fact similar participation by oxygen in acetal hydrolysis has been shown to lower $\Delta G^\ddagger$ by 19 kcal/mol.[30b] The restricted rotations and solvent ordering of **7**[31] could contribute to the more negative $\Delta S^\ddagger$ compared to other oxaziridines.[23a] An alternative ring opening by C–O cleavage would lead to a nitrone. Although more stable than **7**, nitrone formation is an irreversible reaction and was not observed.



7

More definitive experiments to substantiate this mechanism were unsuccessful. These included attempts to prepare optically active **2c** to observe whether racemization occurs with inversion and to trap **7** with added TCNE. In the latter experiments, unfortunately, only unidentifiable products were obtained.

Experimental Section

Instrumentation. Routine proton NMR were run on a Varian Associates A-60A spectrometer, while low-temperature work and NOE experiments were performed on a Bruker AM 300 300-MHz FT spectrometer. IR spectra were taken on a Perkin-Elmer 457 or 727B grating IR spectrometer and mass spectra on an electron-impact VG-MM-Zab-2F spectrometer using a direct probe and 8-kV accelerating voltage.

Materials. Imidates. Methyl *N*-*tert*-butylformimidate (**1a**) was prepared[9b] by alkylation of *N*-*tert*-butylformamide[32] with trimethyloxonium tetrafluoroborate in 74% yield, bp 96 °C [lit.[9b] bp 90–100 °C] or by alkylation with methyl triflate by the procedure for **1c** below. Methyl *N*-methylbenzimidate (**1b**) was prepared by methanolysis of the imidoyl chloride of *N*-methylbenzamide[33] in 34% yield, bp 68–69 °C (6.5 torr) [lit.[10a] 71 °C (5 torr)].

Methyl *N*-*tert*-butylbenzimidate (**1c**) was prepared from *N*-*tert*-butylbenzamide[34] by treating 78.9 g (0.446 mol) in 200 mL of $HCCl_3$ with 150 g (1.27 mol) of methyl fluorosulfonate.[10b] The reaction mixture was stirred for 24 h at room temperature. Removal of solvent and excess methyl fluorosulfonate under vacuum gave a white solid, which was dissolved in 300 mL of CH_2Cl_2 and neutralized with 200 mL of ice-cold 10% NaOH. Evaporation of solvent after drying over NaOH and distillation afforded 46.53 g (54.6%) of methyl *N*-*tert*-butylbenzimidate, bp 56 °C (2.5 torr): IR (neat) ν_{max} 3035 (w), 2980 (s), 1675 (s), 1600 (w), 1390 (s), 1358 (s), 1270 (s), 1200 (m), 1180 (m), 700 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.21 (s, 9 H, *N*-*t*-Bu), 3.62 (s, 3 H, OCH_3), 7.35 (s, 5 H, Ar H).

Methoxyoxaziridines. 2-*tert*-Butyl-3-methoxyoxaziridine (**2a**) was prepared by oxidation of **1a** with a 10% excess of *m*-chloroperbenzoic acid at −40 °C by the method of Aue and Thomas[9b] in 46% yield, bp 59–60 °C (58 torr) [lit.[9b] bp 52 °C (45 torr)].

2-Methyl-3-methoxy-3-phenyloxaziridine (**2b**) was likewise prepared from **1b**. Evaporation of solvent gave a crude product shown by NMR to be 50% methyl benzoate and 45% **2b** with an E/Z ratio of 62:38; ^1H NMR (CCl_4) δ [*E* isomer] 2.36 (s, 3 H, NCH_3), 3.37 (s, 3 H, OCH_3) 7.24–7.46 (m, 5 H, Ar H), [*Z* isomer] 2.87 (s, 3 H, NCH_3), 3.46 (s, 3 H, OCH_3), 7.24–7.46 (m, 5 H, Ar H). However, **2b** was unstable at room temperature, and attempted distillation gave only methyl benzoate as the isolated product.

2-*tert*-Butyl-3-methoxy-3-phenyloxaziridine (**2c**) was similarly prepared from 6.70 g of **1c** at about −10 °C, since oxidation was very slow at −40 °C. Distillation gave 1.6 g (22%) of **2c**, bp 48–50 °C (0.02 torr): IR (neat) ν_{max} 3035 (w), 2980 (s), 1480 (m), 1454 (s), 1365 (s), 1208 (s), 1102 (s), 1031 (m), 770 (s), 705 (s) cm^{-1}; ^1H NMR (CCl_4) δ [*E* isomer] 0.87 (s, 9 H, *N*-*t*-Bu), 3.32 (s, 3 H, OCH_3), 7.23–7.62 (m, 5 H, Ar H), [*Z* isomer] 1.25 (s, 9 H, *N*-*t*-Bu), 3.41 (s, 3 H, OCH_3), 7.23–7.62 (m, 5 H, Ar H); MS (70 eV), *m/e* (relative intensity) 207 (M^+, 0.4), 191 (0.009), 190 (0.1), 177 (4), 176 (4), 151 (22), 150 (34), 136 (3), 119 (12), 105 (88), 77 (58), 71 (4), 57 (35), 56 (100), 51 (22), 41 (28), 39 (11). Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.72. Found: C, 69.54; H, 8.32; N, 6.58.

Optically active **2a** was prepared by adding 1.0 g (0.009 mol) of **1a** in 15 mL of methylene chloride dropwise to a mixture of 2.5 g (0.012 mol) of peroxycamphoric acid[35] and 0.5 g of anhydrous potassium carbonate in 50 mL of CH_2Cl_2 at −40 °C. Workup as before[9b] and vacuum distillation gave 0.249 g (22%) of **2a**, bp 59–60 °C (58 torr); $[\alpha]^{25}_D$ −3.3° (*c* 0.31, $CHCl_3$).

Kinetics. Crystals of pure (*E*)-**2c** (see Results and Discussion) were dissolved in the appropriate solvent containing 10% 1,3,5-trimethylbenzene (v/v) as an internal standard. These solutions were kept frozen (<−18 °C) until brought to temperature equilibration (<7 min) in the NMR probe where temperature was maintained to ±0.9 °C as measured by the difference in chemical

(25) For this effect for aziridines, see: Lehn, J.-M.; Drakenberg, T. *J. Chem. Soc., Perkin Trans. 2* **1972**, 532.
(26) (a) Montanari, F.; Moretti, I.; Torre, G. *Chem. Commun.* **1969**, 1086. (b) Montanari, F.; Moretti, I.; Torre, G. *Gazz. Chim. Ital.* **1973**, *103*, 681.
(27) Lehn, J.-M.; Munsch, B.; Millie, Ph.; Veillard, A. *Theor. Chim. Acta* **1969**, 13, 313.
(28) Bjorgo, J.; Boyd, D. R.; Campbell, R. M.; Thompson, N. J.; Jennings, W. B. *J. Chem. Soc., Perkin Trans. 2* **1976**, 606.
(29) Hermann, H.; Huisgen, R.; Mader, H. *J. Am. Chem. Soc.* **1971**, 1779 and references therein.
(30) (a) Kirby, A. J. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*; Springer-Verlag: New York, 1983. (b) Briggs, A. J.; Evans, C. M.; Glenn, R.; Kirby, A. J. *J. Chem. Soc., Perkin Trans. 2* **1983**, 1637.
(31) Frost, R. G.; Pearson, R. G. *Kinetics and Mechanism*, 2nd ed.; Wiley: New York, 1961; p 135.
(32) Ritter, J. J.; Kalish, J. *J. Am. Chem. Soc.* **1948**, *70*, 4048.
(33) Vaughan, W. R.; Carlson, R. D. *J. Am. Chem. Soc.* **1962**, *84*, 769.
(34) Prajsnar, B.; Troszkiewicz, C. *Rocz. Chem.* **1962**, *36*, 853; *Chem. Abstr.* **1963**, *59*, 504b.
(35) Collins, J. F.; McKervey, M. A. *J. Org. Chem.* **1969**, *34*, 4172.

shifts of an external methanol sample. The E-Z isomerization was followed by NMR integration of the (E)-**2c** *N*-*tert*-butyl signal relative to the integration of the methyl peaks of internal 1,3,5-trimethylbenzene. During the reaction the total methoxy area was invariant, and no evidence of decomposition was observed.

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Registry No. (E)-**1a**, 103202-88-6; (E)-**1b**, 55504-08-0; (E)-**1c**, 103202-89-7; (Z)-**1c**, 103202-90-0; (E)-**2a**, 103202-91-1; (-)-**2a**, 103202-96-6; (E)-**2b**, 103202-92-2; (Z)-**2b**, 103202-93-3; (Z)-**2c**, 103202-94-4; (E)-**2c**, 103202-95-5.

Chiral Recognition in Aqueous Solution. Search for Water-Soluble Chiral Hosts with Apolar Binding Sites

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Macrocycles **1a/b** with tetrasubstituted biphenyl units as chiral barriers are designed as potential hosts for the optical resolution of racemic aromatic guests with anionic residues. Synthetic attempts to prepare from a planar arene, pyrene, a chiral biphenyl barrier incorporated into a water-soluble host are presented. On the way to such a macrocycle, the 1,7,20,26-tetraoxa[8](4,5)phenanthreno[8.1]paracyclophane **7** was synthesized. Selective ozonolysis of the 9,10-bond of the phenanthrene unit of **7** to generate the chiral barrier was not successful. The phenanthrene unit, according to ^{1}H NMR, is located in the intramolecular cavity of **7** and therefore is protected from attack by ozone. On the way to **1a**, the 1,7,20,26-tetraoxa[7](2,2′)biphenylo[7.1]paracyclophane **14** with two aminomethyl groups at the 6,6′-positions of the biphenyl unit was prepared. Eschweiler–Clarke methylation of **14** afforded as major product, besides the macrocyclic tris(tertiary amine) **15**, the precursor to **1a**, a macrocycle incorporating a 6,7-dihydro-5*H*-dibenz[*c*,*e*]azepine moiety. A possible mechanism of formation of the 1,7,19,25-tetraoxa[7](1,11)-5*H*-dibenz[*c*,*e*]azepino[7.1]paracyclophane **18** is presented. The synthesis of 1′-ethyl-12,15-bis((diethylamino)methyl)-28,32,36,38-tetramethylspiro[1,7,20,26-tetraoxa[7](2,2′)biphenylo[7.1]-paracyclophane-33,4′-piperidine] (**20**) as nonquaternized precursor to **1b** is described. Binding studies in acidic aqueous solution with the triprotonated macrocyclic amines **15** and **20** below their critical micelle concentration showed that these macrocycles do not act as hosts for apolar guests.

Optically active molecular hosts and their uses in the separation of guest enantiomers through complexation in crystallization, distribution, transport, and chromatographic experiments have attracted considerable interest during the past years.[3-13] Most studies in organic solvents describe the chiral recognition of cationic guests by chiral crown ligands. In aqueous solution, cyclodextrins have almost exclusively been used to resolve racemic compounds that bind with their apolar residues to the cavity.[14-16] Only one report describes the formation of diastereomeric host–guest complexes in aqueous solution by a fully synthetic, optically active host.[17]

During the past 5 years, we have prepared water-soluble achiral hosts which form stable complexes with apolar, especially aromatic, guests in aqueous solution.[18,19] Based on the results of our complexation studies, we designed the macrocyclic host **1** for resolving racemic aromatic guests with anionic residues through complexation in aqueous solution. Guests that we had hoped to resolve are aromatic α-amino acids, aromatic carboxylic acids such as mandelic acid and atrolactic acid, and especially α-arylpropionic acids, some of which are important drugs (e.g., ibuprofen [2-(4-isobutylphenyl)propionic acid] and naproxen [2-(6-methoxy-2-naphthyl)propionic acid (**2**)]).[20] Macrocycle **1** incorporates a 2,2′,6,6′-tetrasubstituted biphenyl unit as

(1) University of California, Los Angeles.
(2) Max-Planck-Institute for medical research, Heidelberg.
(3) Cram, D. J.; Cram, J. *Acc. Chem. Res.* **1978**, *11*, 8-14.
(4) Lehn, J. M. *Science (Washington, D.C.)* **1985**, *227*, 849-856.
(5) Jolley, S. T.; Bradshaw, J. S.; Izatt, R. M. *J. Heterocycl. Chem.* **1982**, *19*, 3-19.
(6) Prelog, V.; Mutak, S. *Helv. Chim. Acta* **1983**, *66*, 2274-2278.
(7) Naemura, K.; Ebashi, I.; Nakazaki, M. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 767-768.
(8) Stoddart, J. F. In *Progress in Macrocyclic Chemistry*; Izatt, R. M., Christensen, J. J., Eds.; Wiley: New York, 1981; Vol. 2, pp 173-250.
(9) Rebek, J., Jr.; Costello, T.; Marshall, L.; Wattley, R.; Gadwood, R. C.; Onan, K. *J. Am. Chem. Soc.* **1985**, *107*, 7481-7487.
(10) Pearson, D. P. G.; Leigh, S. J.; Sutherland, I. O. *J. Chem. Soc., Perkin Trans. 1* **1979**, 3113-3126.
(11) Yamamoto, K.; Fukushima, H.; Okamoto, Y.; Hatada, K.; Nakazaki, M. *J. Chem. Soc., Chem. Commun.* **1984**, 1111-1112.
(12) Kellogg, R. M. *Top. Curr. Chem.* **1982**, *101*, 111-145.
(13) Canceill, J.; Lacombe, L.; Collet, A. *J. Am. Chem. Soc.* **1985**, *107*, 6993-6996.
(14) Bender, M. L.; Komiyama, M. *Cyclodextrin Chemistry*; Springer: Berlin, 1978.
(15) For some recent examples, see: (a) Mikolajczyk, M.; Drabowicz, J. *J. Am. Chem. Soc.* **1978**, *100*, 2510-2515. (b) Yamanari, K.; Shimura, Y. *Chem. Lett.* **1982**, 1957-1958.
(16) For examples of the use of cyclodextrins in chromatographic separations of enantiomers, see: (a) Debowski, J.; Sybilska, D.; Jurczak, J. *J. Chromatogr.* **1982**, *237*, 303-306. (b) Armstrong, D. W.; DeMond, W.; Czech, B. P. *Anal. Chem.* **1985**, *57*, 481-484. (c) Armstrong, D. W.; Ward, T. J.; Czech, A.; Czech, B. P.; Bartsch, R. A. *J. Org. Chem.* **1985**, *50*, 5556-5559.
(17) Takahashi, I.; Odashima, K.; Koga, K. *Tetrahedron Lett.* **1984**, *25*, 973-976.
(18) (a) Diederich, F.; Dick, K. *J. Am. Chem. Soc.* **1984**, *106*, 8024-8036. (b) Diederich, F.; Griebel, D. *J. Am. Chem. Soc.* **1984**, *106*, 8037-8046. (c) Diederich, F.; Dick, K.; Griebel, D. *Chem. Ber.* **1985**, *118*, 3588-3619.
(19) Diederich, F.; Dick, K.; Griebel, D. *J. Am. Chem. Soc.* **1986**, *108*, 2273-2286.
(20) Giordano, C.; Castaldi, G.; Uggeri, F. *Angew. Chem.* **1984**, *96*, 413-419; *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 413-419.

0022-3263/86/1951-3270$01.50/0