with distilled water into a 50-ml. separatory funnel containing petroleum ether. The petroleum ether layer was extracted with cold, dilute nitric acid, and the chloride content of the aqueous solution was determined by the Volhard method. The initial concentration of diethylamine was determined by titration of a 5-ml. aliquot of the benzene solution with standard hydrochloric acid with methyl red as indicator. In the runs with N-methyl-aniline the reaction mixture was washed out with acetic acid, and the amine concentration determined by titration with a standard solution of perchloric acid in acetic acid with methyl violet as indicator.[33] Some runs were followed by potentiometric titration of the weak organic bases in glacial acetic acid with standard perchloric acid. The results obtained by this method agreed well with those obtained by potentiometric titration of chloride ion with standard silver nitrate.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY, CAMBRIDGE 39, MASS.]

Molecular Asymmetry of Olefins. II. The Absolute Configuration of trans-Cyclooctene[1,2]
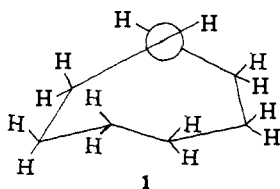
BY ARTHUR C. COPE AND ANIL S. MEHTA[3]

The absolute configuration of trans-cyclooctene has been determined and the levorotatory enantiomer is assigned the (R)-configuration. (1S:2S)-(+)-1,2-Dimethoxycyclooctane was synthesized from (2R:3R)-(+)-tartaric acid and its rotation was shown to be identical with that of the same diether obtained from (−)-trans-cyclooctene.

Although it has long been recognized that trans cyclic olefins of medium ring size should exhibit molecular asymmetry[4] the first resolution of such an olefin was reported only recently.[5] trans-Cyclooctene was resolved as the trans-dichloro(trans-cyclooctene)-(α-methylbenzylamine)platinum(II) complex containing optically active α-methylbenzylamine. The object of the present work was to assign absolute configurations to the enantiomeric trans-cyclooctenes.

(−)-trans-Cyclooctene was treated with osmium tetroxide and the resulting osmate ester was decomposed with sodium sulfite to give (+)-trans-1,2-cyclooctanediol-(10).[6] Methylation of the glycol 10 with diazomethane in the presence of fluoroboric acid[7] afforded trans-1,2-dimethoxycyclooctane (9) having $[\alpha]^{31}D + 49.5°$ (c 4.337, chloroform).

The same compound of known absolute configuration (1S:2S)-(+)-1,2-dimethoxycyclooctane (9) $[[\alpha]^{31.8}D +50.3°$ (c 4.63, chloroform)] was synthesized from (2R:3R)-(+)-tartaric acid (2) by the sequence of reactions summarized in Fig. 1.[8] Since the signs of rotation of the relay compounds 9 were the same, it followed that (−)-trans-cyclooctene was related to (2R:3R)-(+)-tartaric acid and has the (R)-configuration as indicated in the Newman projection formula 1.

1

The synthesis of (1S:2S)-(+)-1,2-dimethoxycyclooctane (9) involved use of the C_2- and C_3-hydroxyl groups of (2R:3R)-(+)-tartaric acid (2) as the source of the adjacent trans-methoxyl groups in 9.

(2R:3R)-(+)-Tartaric acid was esterified[9] by methanolic hydrogen chloride and the resulting dimethyl (2R:3R)-(+)-tartrate was methylated[10] with methyl iodide and silver oxide. Lithium aluminum hydride reduction of dimethyl (2R:3R)-(+)-2,3-dimethoxysuccinate (3) using the minimum amount of aqueous base for decomposition of the aluminate salt[11] gave (2S:3S)-(+)-2,3-dimethoxy-1,4-butanediol[12] (4a) in 62% yield. The crystalline ditosylate 4b[12] was prepared (94% yield) and converted to the diiodide (2R:3R)-(−)-2,3-dimethoxy-1,4-diiodobutane[12] (4e) by treatment with sodium iodide in anhydrous acetone (94% yield).

Alkylation of acetonitrile with either the ditosylate 4b or the diiodide 4e gave a poor yield of the 'dinitrile 5c; the major product appeared to be trans-3,4-dimethoxycyclopentyl cyanide. Attempts to alkylate 4b or 4e with lithium ethoxyacetylene to give a diyne that on hydrolysis would give the dicarboxylic ester 5e also were unsuccessful.

Posternak and Susz[12] on attempting the conversion of the diiodide 4e to the dinitrile 4c with sodium cyanide were able to obtain only a difficultly separable mixture consisting essentially of an iodonitrile (from the iodine and nitrogen content) and a small amount of the desired dinitrile which was not analyzed. No experimental details were given. In this work the dinitrile 4c was obtained by the reaction of the ditosylate 4b with sodium cyanide under carefully controlled conditions. Optimum yields (65–78%) were obtained with purified dimethyl sulfoxide as solvent and a reaction time of 6 days at 20 ± 3°. Higher temperatures gave markedly lower yields and made purification more difficult. Other solvents (acetone, methanol, or dimethylformamide) gave either a good recovery of the starting material or a poor yield of the product.

(1) For a preliminary communication on this work see A. C. Cope and A. S. Mehta, J. Am. Chem. Soc., 86, 1268 (1964).

(2) Supported in part by the Army Research Office (Durham) under Grant No. DA-ARO(D)31-124-G404.

(3) Postdoctoral Fellow, 1963–1964.

(4) A. T. Blomquist, L. H. Liu, and J. C. Bohrer, J. Am. Chem. Soc., 74, 3643 (1952); V. Prelog in A. Todd, Ed., "Perspectives in Organic Chemistry," Interscience Publishers, Inc., New York, N. Y., 1956, p. 129.

(5) A. C. Cope, C. R. Ganellin, H. W. Johnson, Jr., T. V. Van Auken, and H. J. S. Winkler, J. Am. Chem. Soc., 85, 3276 (1963).

(6) A. C. Cope, R. A. Pike, and C. F. Spencer, ibid., 75, 3212 (1953).

(7) M. Neeman, M. C. Caserio, J. D. Roberts, and W. S. Johnson, Tetrahedron, 6, 36 (1959).

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(9) A. Skrabal and L. Hermann, Monatsh., 43, 633 (1922).

(10) T. Purdie and J. C. Irvine, J. Chem. Soc., 79, 957 (1901).

(11) V. M. Mićović and M. Lj. Mihailović, J. Org. Chem., 18, 1190 (1953).

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The dibasic ester **4d** was obtained from the dinitrile in 90% over-all yield by methanolysis followed by hydrolysis of the intermediate bisimidoester hydrochloride. Reduction of the dicarboxylic ester with lithium aluminum hydride afforded the $(3S:4S)$-(−)-3,4-dimethoxy-1,6-hexanediol (**5a**) from which a crystalline ditosylate **5b** was obtained in 83% yield. Treatment of the ditosylate **5b** with sodium cyanide in dimethyl sulfoxide gave the dinitrile **5c** (87% yield). The regulation of the temperature in this displacement was not as critical as for the lower homolog **4b**. The dinitrile **5c** was converted to dimethyl $(4S:5S)$-(−)-4,5-dimethoxysuberate (**5d**) in 87% yield.

Under the conditions of the acyloin condensation the dicarboxylic ester **5d** did not yield any of the desired $(5S:6S)$-2-hydroxy-*trans*-5,6-dimethoxycyclooctanone.[13] The major product isolated, 2-carbomethoxy-*trans*-4,5-dimethoxycycloheptanone (**6c**, 31%), resulted from a Dieckmann condensation. The product also contained *trans*-4,5-dimethoxycycloheptanone (**6a**, 6%), the unchanged dicarboxylic ester (5.6%), and an unidentified compound (1%). Variation in the amount of sodium gave little change in the products. Dimethyl suberate, however, under identical conditions gave a 59% yield of 2-hydroxycyclooctanone. This difference in reactivity is attributed to the participation of the methoxyl groups in interactions of the type
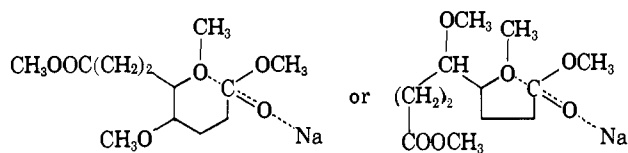
Thus the requirement that both carbomethoxy groups be on the sodium surface at the same time for the acyloin condensation is not easily met by the dimethoxydicarboxylic ester, and a Dieckmann condensation can readily take place instead as soon as a trace of sodium methoxide is formed in the mixture.[14] The ketone **6a** is presumed to arise from hydrolysis and decarboxylation of **6c** during the isolation procedure.

Hydrolysis of $(4S:5S)$-2-carbomethoxy-*trans*-4,5-dimethoxycycloheptanone gave $(4S:5S)$-(+)-4,5-dimethoxycycloheptanone (**6a**). However, a better yield (50%) of **6a** was obtained by Thorpe–Ziegler cyclization of the dinitrile **5c** followed by acid hydrolysis of the β-ketonitrile **6b**.

The cycloheptanone **6a** was converted to the cyanohydrin **7a** which was hydrogenated catalytically. The resulting aminoalcohol **7b** on treatment with sodium nitrite and acetic acid yielded $(4S:5S)$-(+)-4,5-dimethoxycyclooctanone (**8**, 23% from ketone **6a**). Wolff–Kishner reduction of the cyclooctanone **8** gave $(1S:2S)$-(+)-1,2-dimethoxycyclooctane (**9**, 76% yield).

Thus, $(2R:3R)$-(+)-tartaric acid (**2**) has been related to (−)-*trans*-cyclooctene and the only assumption in assignment of the (R)-configuration to the olefin is that osmium tetroxide attacks from the side of the double bond not hindered by the ring methylene

Fig. 1.—Synthesis of $(1S:2S)$-(+)-1,2-dimethoxycyclooctane.

groups. In the osmium tetroxide oxidation of 5α,22a-spirost-2-ene it has been reported[15] that the product is the 2α,3α-diol which results from the approach of the reagent to the $\Delta^{2,3}$-bond from the less hindered α-side of the steroidal nucleus.

The results obtained are contrary to those of Moscowitz and Mislow[16] who reported on the basis of theoretical considerations that the (−)-enantiomer of *trans*-cyclooctene has the (S)-configuration.

Experimental[17]

(13) The procedure was similar to that of N. L. Allinger, *Org. Syn.*, **36**, 79 (1956).

(14) A similar result was reported in the attempted acyloin cyclization of diethyl γ,γ-ethylenedioxypimelate; P. D. Gardner, G. R. Haynes, and R. L. Brandon, *J. Org. Chem.*, **22**, 1206 (1957). See also N. J. Leonard, L. A. Miller, and J. W. Berry, *J. Am. Chem. Soc.*, **79**, 1482 (1957).
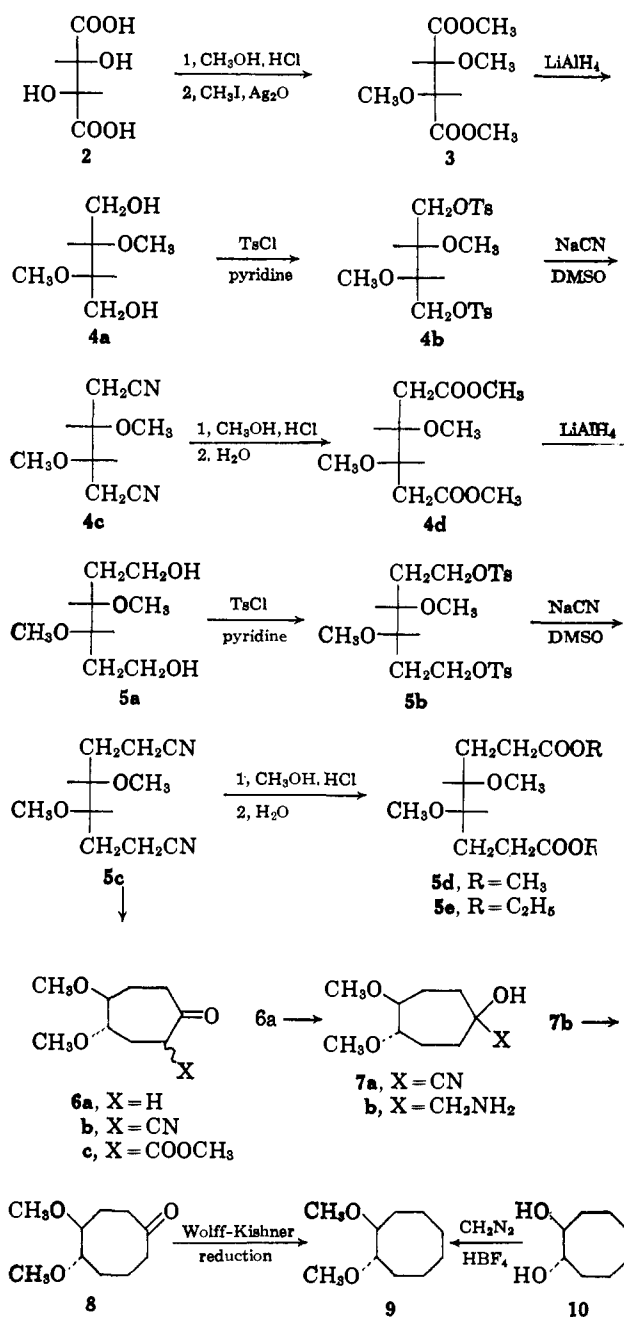
(15) C. Djerassi, L. B. High, T. T. Grossnickle, R. Ehrlich, J. A. Moore, and R. B. Scott, *Chem. Ind.* (London), 474 (1955).

(16) A. Moscowitz and K. Mislow, *J. Am. Chem. Soc.*, **84**, 4605 (1962).

(17) Melting points are corrected and boiling points are uncorrected. Microanalyses were performed by the Scandanavian Microanalytical Laboratory, Herlev, Denmark, or by S. M. Nagy and his associates. Nuclear magnetic resonance (n.m.r.) spectra were recorded with a Varian Associates A-60 instrument with tetramethylsilane as the internal standard (τ = 10.00).

by esterification with methanol and hydrogen chloride. The ester was obtained in 59% yield, b.p. 115 (0.06 mm.)-125° (1.0 mm.), m.p. 47-48° [lit.[9] b.p. 159° (12 mm.), m.p. 48°], $[\alpha]^{22.5}$D +4.81° (c 9.35, ethanol).

Dimethyl (2R:3R)-(+)-2,3-dimethoxysuccinate (3) was prepared[10] from dimethyl (+)-tartrate, methyl iodide, and silver oxide. The product, obtained as a colorless oil in 93% yield, had b.p. 135-137° (13 mm.) [lit. b.p. 132° (12 mm.), m.p. 51°,[10] b.p. 130-132° (12 mm.)[18]]. This oil did not crystallize as reported by Purdie and Irvine.[10] However, Schmidt and Zeiser[18] also were unable to crystallize the same ester made from (+)-tartaric acid and diazomethane.

The infrared spectrum of 3 in carbon tetrachloride unexpectedly displayed two bands in the carbonyl region (1735 and 1760 cm.$^{-1}$). The same compound prepared by a modification of the above procedure (using silver tartrate instead of dimethyl tartrate) had an identical infrared spectrum. Its n.m.r. spectrum showed three singlets at 5.91 (2H), 6.25 (6H), and 6.59 τ (6H).

Anal. Calcd. for $C_8H_{14}O_6$: C, 46.60; H, 6.84. Found: C, 46.91; H, 7.05.

(2S:3S)-(+)-2,3-Dimethoxy-1,4-butanediol (4a).—To a cooled, stirred suspension of lithium aluminum hydride (59 g.) in 1.5 l. of anhydrous ether was added dropwise a solution of 170 g. of the dicarboxylic ester 3 in 1.5 l. of ether. The mixture was stirred overnight at room temperature, then ice-cooled and decomposed by successive addition of 59 ml. of water, 59 ml. of 15% sodium hydroxide solution, and 177 ml. of water.[11] After stirring 1 hr. longer the mixture was filtered, the filter cake was washed several times with acetone (the glycol is sparingly soluble in ether), and the combined filtrates were evaporated to dryness. The residual oil was distilled yielding 77.2 g. (62%) of (2S:3S)-(+)-2,3-dimethoxy-1,4-butanediol, b.p. 101 (0.1 mm.)-105° (0.08 mm.). The glycol is extremely hygroscopic. It crystallized on cooling and could be recrystallized by dissolving in a minimum amount of chloroform, cooling to 0°, and adding an equal volume of anhydrous ether. The recrystallized alcohol had m.p. 37-38°, $[\alpha]^{25}_{578}$ + 6.32°, $[\alpha]^{25}_{546}$ + 7.17°, $[\alpha]^{25}$D calculated from the preceding rotations +6.06° (c 8.23, ethanol); n.m.r. (CDCl₃): 6.24 (4H, broad), 6.46 τ (10H, singlet superimposed on a broad peak). Addition of 1 drop of pyridine shifted the hydroxyl proton resonance, and the spectrum showed 5.95 (2H, singlet), 6.22 (4H, multiplet), 6.46 τ (8H, singlet on a small broad peak).

Posternak and Susz[12] prepared the same compound as an oil, b.p. 92-97° (0.10 mm.), $[\alpha]^{21}$D +5.1° (c 5.5, alcohol). In their preparation, after lithium aluminum hydride reduction of dimethyl (+)-2,3-dimethoxysuccinate, the product was isolated as the acetyl derivative and saponified with methanolic barium hydroxide.

(2S:3S)-(+)-2,3-Dimethoxy-1,4-butanediol Di-p-toluenesulfonate (4b).—To a stirred solution of 60 g. of glycol 4a in 300 ml. of pyridine cooled to −20° was added 184 g. of p-toluenesulfonyl chloride over 0.5 hr. The mixture was allowed to stand overnight at room temperature, and then poured onto crushed ice, extracted with ether, and the etheral solution was washed with dilute hydrochloric acid, aqueous sodium bicarbonate, and water. The organic extracts were dried over magnesium sulfate, filtered, and evaporated to a pale yellow crystalline residue. Recrystallization from ether gave 171.2 g. (94%) of (2S:3S)-(+)-2,3-dimethoxy-1,4-butanediol di-p-toluenesulfonate, m.p. 65° [lit.[12] 65-66°, $[\alpha]^{24}$D +5.0° (c 3.62, chloroform)]. The ditosylate 4b showed $[\alpha]^{27.5}$D +9.02° (c 4.635, chloroform); n.m.r. (CDCl₃): 2.24 (4H, doublet, J = 8 c./sec.), 2.67 (4H, doublet, J = 8 c./sec.), 5.9 (4H, doublet, J = 4.3 c./sec.), 6.5 (2H, triplet, J = 4.3 c./sec.), 6.73 (6H, singlet), 7.58 τ (6H, singlet).

Anal. Calcd. for $C_{20}H_{26}S_2O_8$: C, 52.38; H, 5.72; S, 13.99. Found: C, 52.35; H, 5.70; S, 13.98.

(2R:3R)-(−)-2,3-Dimethoxy-1,4-diiodobutane (4e).—Ten grams of ditosylate 4b and 17 g. of dry sodium iodide in 150 ml. of anhydrous acetone were heated at reflux temperature for 36 hr. The solution was decanted from the precipitated sodium tosylate and the latter was washed with acetone and ether. The combined solutions were evaporated to dryness at 20 mm. and the residue

was taken up in water and extracted with ether. The etheral solution was washed with aqueous sodium thiosulfate, sodium carbonate, and water. After drying over magnesium sulfate and evaporation of the solvent, the residue was distilled, yielding 7.6 g. (94%) of diiodide, b.p. 73-75° (0.05 mm.), n^{18}D 1.5729 [lit.[12] b.p. 64-70° (0.045 mm.), n^{18}D 1.5730].

(3S:4S)-(+)-3,4-Dimethoxy-1,6-hexanedinitrile (4c).—To a stirred solution of 72.48 g. of ditosylate 4b in 400 ml. of dimethyl sulfoxide (distilled from calcium hydride) was added 19.24 g. of sodium cyanide in small amounts over a period of 3 days. The temperature of the mixture was kept at 20 ± 3°. At the end of 6 days the clear brown solution was poured into 2 l. of water and extracted with three 1.2-l. portions of methylene chloride. After washing the organic extracts with three 400-ml. portions of water and drying over magnesium sulfate, the solvent was removed under reduced pressure. The crystalline residue (25 g.) was recrystallized from ether-benzene affording 17.2 g. (65%) of (3S:4S)-(+)-3,4-dimethoxy-1,6-hexanedinitrile, m.p. 71.8-72.2°. The dinitrile could be distilled, b.p. 121-122° (0.3 mm.), and had $[\alpha]^{27.5}$D +15.81° (c 8.415, acetone); n.m.r. (CDCl₃): 6.28 (2H, essentially a triplet J = 5 c./sec. with further fine splitting), 6.5 (6H, singlet), 7.34 τ (4H, doublet, J = 5 c./sec.).

Anal. Calcd. for $C_8H_{12}N_2O_2$: C, 57.13; H, 7.19; N, 16.66. Found: C, 57.10; H, 7.23; N, 16.66.

This reaction was conducted with various solvents, temperatures, and times. Using dimethyl sulfoxide as solvent the highest yield obtained was 78% and in most cases the infrared spectrum of the mother liquors after recrystallization showed bands for the nitrile and p-toluenesulfonyl groups. Temperature control was important, as above 25° the reaction mixture turned black and the resulting dinitrile could be purified only by chromatography (Merck acid-washed alumina using 90% benzene-10% chloroform as eluent).

Dimethyl (3S:4S)-(−)-3,4-Dimethoxyadipate (4d).—A stirred solution of 27.6 g. of dinitrile 4c in 800 ml. of anhydrous methanol was saturated with dry hydrogen chloride at room temperature. The mixture was heated at reflux temperature for 2 hr.; a white precipitate formed after 1 hr. About half of the methanol was distilled, 120 ml. of water was added, and the solution was left overnight at room temperature. After extraction of the mixture with methylene chloride, drying over magnesium sulfate, and removal of solvent, an oily residue was obtained, composed principally of the dicarboxylic ester 4d containing some of the corresponding acid, according to its infrared spectrum. For esterification of the acid present, a solution was prepared by adding 15 ml. of thionyl chloride with stirring to 100 ml. of methanol cooled to −20° and kept below −10° during the addition. The oil obtained above was added and the mixture was allowed to warm to room temperature and then kept at 35-40° for 2 hr. All of the low-boiling components were removed by evaporation under reduced pressure. The residue was dissolved in ether and washed with 5% sodium bicarbonate solution and water. The solvent was removed from the dried ether extracts. Distillation of the residue gave 34.74 g. (91%) of dimethyl (3S:4S)-(−)-3,4-dimethoxyadipate. The ester had b.p. 85° (0.06 mm.), n^{25}D 1.4351; $[\alpha]^{27.5}$D −23.55° (c 7.05, acetone); n.m.r. (CDCl₃): 6.04 (2H, multiplet), 6.24 (6H, singlet), 6.53 (6H, singlet), 7.47 τ (4H, multiplet).

Anal. Calcd. for $C_{10}H_{18}O_6$: C, 51.27; H, 7.75. Found: C, 51.37; H, 7.74.

(3S:4S)-(−)-3,4-Dimethoxy-1,6-hexanediol (5a).—To a cooled stirred suspension of 12.5 g. of lithium aluminum hydride in 400 ml. of tetrahydrofuran was added dropwise a solution of 34.6 g. of dimethyl (3S:4S)-(−)-3,4-dimethoxyadipate in 250 ml. of tetrahydrofuran. On completion of the addition the mixture was stirred for 2 hr. and then refluxed for 30 min. After cooling in ice the mixture was decomposed by dropwise addition of 12.5 ml. of water and 12.5 ml. of 15% sodium hydroxide solution followed by 37.5 ml. of water, and was stirred for 3 hr. After filtration and washing the filter cake several times with tetrahydrofuran, the solvent was removed under reduced pressure and the oil was dried at 40° (0.1 mm.). The residue weighed 26.3 g. which corresponded to the theoretical yield of the glycol. It was extremely hygroscopic and decomposed on prolonged heating during distillation and so was used without purification for the next step of the synthesis. A small amount was distilled in a short-path still (bath temperature about 120°, 0.1 mm.) to obtain an analytical sample. The glycol had n^{25}D 1.4540; $[\alpha]^{27}$D −74.49° (c 5.965, acetone); n.m.r. (CDCl₃): 6.2 (4H, triplet, J = 6 c./sec.), 6.5 (8H, singlet superimposed on broad peak), 6.72

Mass spectra were determined with a C.E.C. 21-130 mass spectrometer (inlet temperature 150°, ionizing potential 68 e.v.). Optical rotations were determined with a Zeiss polarimeter which gave a value at the sodium D line (589.2 mμ) and with a Zeiss photoelectric polarimeter which gave values at 546.1 and 577.8 mμ. For the latter instrument the value at the sodium D line was calculated by extrapolation using the first approximation of Drude's formula for normal rotation dispersion.

(18) O. Th. Schmidt and H. Zeiser, *Ber.*, **67**, 2120 (1934).

(2H, broad singlet), 8.18 τ (4H, essentially a triplet $J = 6$ c./sec. with fine splitting). Upon addition of 1 drop of pyridine a shift from 6.72 to 5.75 τ (2H, singlet) was observed in the hydroxyl proton band.

Anal. Calcd. for $C_8H_{18}O_4$: C, 53.91; H, 10.18. Found: C, 53.83; H, 10.14.

(3*S*:4*S*)-(−)-**3,4-Dimethoxy-1,6-hexanediol Di-*p*-toluenesulfonate (5b).**—The crude glycol (25.9 g.) obtained above was dissolved in pyridine, the solution cooled to −20°, and 100 g. of *p*-toluenesulfonyl chloride was added. The mixture was stirred overnight at room temperature and then was poured into about 800 ml. of ice-water. The ditosylate precipitated immediately and was filtered, washed well with cold water, and dried over phosphorus pentoxide at 0.1 mm. for 24 hr. The ditosylate **5b** (58.6 g., 83% yield) had m.p. 66.2–66.8°, $[\alpha]^{27}$D −28.76° (*c* 4.485, acetone); n.m.r. (CDCl₃): 2.05 (4H, doublet, $J = 8.5$ c./sec.), 2.52 (4H, doublet, $J = 8.5$ c./sec.), 5.8 (4H, multiplet), 6.68 (8H, singlet superimposed on multiplet), 7.51 (6H, singlet), 8.23 τ (4H, multiplet).

Anal. Calcd. for $C_{22}H_{30}O_8S_2$: C, 54.30; H, 6.22; S, 13.18. Found: C, 54.21; H, 6.27; S, 12.94.

(4*S*:5*S*)-(−)-**4,5-Dimethoxy-1,8-octanedinitrile (5c).**—A solution of 19.73 g. of the ditosylate **5b** and 4.63 g. of sodium cyanide in 250 ml. of dimethyl sulfoxide was stirred at room temperature for 5 days. The pale yellow solution was poured into 2 l. of water and extracted with three 1-l. portions of methylene chloride. The organic extracts were washed with three 300-ml. portions of water, dried over magnesium sulfate, and filtered. After removal of the solvent the residue was distilled, giving 6.9 g. (87%) of (4*S*:5*S*)-(−)-4,5-dimethoxy-1,8-octanedinitrile, b.p. 135–137° (0.35 mm.), n^{25}D 1.4482, $[\alpha]^{28.2}$D −76.28° (*c* 7.635, acetone); n.m.r. (CDCl₃): 6.53 (8H, singlet under multiplet), 7.45 (4H, mainly a triplet, $J = 7$ c./sec.), 8.2 τ (4H, multiplet).

Anal. Calcd. for $C_{10}H_{16}O_2N_2$: C, 61.20; H, 8.22; N, 14.28. Found: C, 61.28; H, 8.20; N, 14.20.

Dimethyl (4*S*:5*S*)-(−)-4,5-Dimethoxysuberate (5d).—A solution of 6.75 g. of the dinitrile **5c** in 100 ml. of anhydrous methanol was saturated with dry hydrogen chloride at room temperature. The mixture was heated at reflux temperature for 2 hr. during which time a white precipitate was formed. Half of the methanol was removed by distillation, 20 ml. of water was added, and the mixture was kept overnight at room temperature. Extraction with methylene chloride and removal of the solvent from the dried extract left an oil which was shown by infrared spectroscopy to be mainly the ester with a small amount of the corresponding acid. The mixture was esterified with thionyl chloride and methanol and the product was isolated in the manner described for compound **4d**. Two successive distillations yielded 7.8 g. (87%) of dimethyl (4*S*:5*S*)-(−)-4,5-dimethoxysuberate as a colorless oil, b.p. 104–106° (0.08 mm.), n^{25}D 1.4403, $[\alpha]^{28.8}$D −37.57° (*c* 5.51, acetone); n.m.r. (CDCl₃): 6.25 (6H, singlet), 6.53 (8H, singlet superimposed on multiplet), 7.5 (4H, multiplet), 8.17 τ (4H, multiplet).

Anal. Calcd. for $C_{12}H_{22}O_6$: C, 54.95; H, 8.45. Found: C, 54.83; H, 8.32.

(4*S*:5*S*)-(+)-**4,5-Dimethoxycycloheptanone (6a).**—To a stirred refluxing mixture of 1.77 g. of lithium wire in 1.2 l. of anhydrous ether 20.2 g. of bromobenzene was added during 2 hr. in a high dilution apparatus under nitrogen. After heating under reflux for 1 hr., 18.9 g. of N-methylaniline was added during 20 min., followed by a solution of 2.6 g. of the dinitrile **5c** in 300 ml. of ether during 48 hr. The mixture was cooled to room temperature, decomposed by successive addition of 80 ml. of 2 *N* and 40 ml. of 6 *N* hydrochloric acid, and stirred for 2 hr. to hydrolyze the imine. The water layer was separated, extracted with ether, and the combined organic layers were dried and the low-boiling components removed by distillation at 40° (0.1 mm.). The residual oil (3.3 g.) was chromatographed on 50 g. of silicic acid (Mallinckrodt reagent, 100 mesh), and 2-cyano-*trans*-4,5-dimethoxycycloheptanone (**6b**, 2.29 g., 88%) was obtained as a crystalline solid eluted with carbon tetrachloride–chloroform mixtures. If the chromatography was done carefully the compound appeared on the column as two distinct bands; the first is eluted with carbon tetrachloride–chloroform 3:2 and the second with carbon tetrachloride–chloroform 2:3. These two isomers of the ketonitrile **6b** are obtained in approximately equal amounts and have essentially identical infrared spectra and similar behavior on thin-layer and gas chromatography. The infrared spectra showed bands at 2820, 1100 (–OCH₃), 2250 (–C≡N), and 1720 (–C=O) cm.$^{-1}$.

To 2.0 g. of the ketonitrile **6b** (shown to be pure by gas chromatography) was added 50 ml. of 30% sulfuric acid (by weight) and the mixture was heated at the reflux temperature for 18 hr. The solution was extracted with three 100-ml. portions of ether and each extract was washed successively with 10 ml. of saturated aqueous sodium chloride solution. The residue from the combined dried organic extracts after removal of solvent was distilled in a short-path still (bath temperature up to 100°, 0.2 mm.), giving 1.0 g. (57%) of (4*S*:5*S*)-(+)-4,5-dimethoxycycloheptanone.[19] The cycloheptanone **6a** had $[\alpha]^{30}_{578}$ +116.2°, $[\alpha]^{30}_{546}$ + 134.9°, $[\alpha]^{30}$D (calculated from the preceding rotations) +110.7° (*c* 4.60, chloroform); n.m.r. (CDCl₃): 6.5 (2H, multiplet), 6.66 (6H, singlet), 7.4 (2H, multiplet), 7.71 (2H, triplet, $J = 4.2$ c./sec.), 8.1 τ (4H, multiplet). The mass spectrum showed a molecular ion peak at m/e 172 and principal fragment peaks at m/e 140, 127, 114, 72, 71, 55, 54, 41.

Anal. Calcd. for $C_9H_{16}O_3$: C, 62.76; H, 9.36. Found: C, 62.63; H, 9.39.

(4*S*:5*S*)-(+)-**4,5-Dimethoxycyclooctanone (8).**—To a stirred ice-cooled mixture of 1.0 g. of the ketone **6a** and 0.516 g. of potassium cyanide in 0.8 ml. of water was added 1.34 ml. of 40% sulfuric acid during 30 min. After stirring for 24 hr., 8.0 ml. of water was added, and the mixture was extracted with three 30-ml. portions of ether. The combined ether extracts were washed with water, dried, and the solvent was removed. The residual oil (1.18 g.) showed infrared bands for OH (3580, 3400 cm.$^{-1}$), —C≡N (2235 cm.$^{-1}$), OCH₃ (1100 cm.$^{-1}$), and a very weak C=O band (1695 cm.$^{-1}$).

Without purification the cyanohydrin was hydrogenated catalytically at room temperature and atmospheric pressure. Platinum oxide (0.27 g.) in 5 ml. of glacial acetic acid was reduced and the cyanohydrin **7a** in 15 ml. of glacial acetic acid was added. The uptake of hydrogen was 10.4 mmoles. The solution was filtered, the catalyst was washed with water, and the filtrate was made up to 200 ml. with water and cooled to 0°. A solution of 2.21 g. of sodium nitrite in 12 ml. of water was added during 15 min. and the mixture was stirred for 4 hr. at 0° and kept overnight at room temperature. Sodium carbonate was added to neutralize the acid and the mixture was extracted with three 300-ml. portions of ether. The oil remaining (0.8 g.) after removal of solvent from the dried ether extracts was partially separated into two fractions by gas chromatography (silicone oil, 140°). The infrared spectrum of the first peak, later found to be a mixture of two components, showed hydroxyl and carbonyl absorption. The second peak was the desired cyclooctanone **8**. Better separation and recovery were achieved by column chromatography. The original mixture (0.627 g.) was chromatographed on 7.0 g. of silicic acid and eluted with carbon tetrachloride–chloroform mixtures. Eluting with 10–25% chloroform in carbon tetrachloride gave a mixture of 0.035 g. of the cycloheptanone **6a** and the cyclooctanone **8**. Further elution with chloroform–carbon tetrachloride (3:7) gave 0.2 g. of the desired (4*S*:5*S*)−(+)-4,5-dimethoxycyclooctanone (**8**) as a crystalline solid. Further elution while increasing the polarity of the solvent mixture from chloroform–carbon tetrachloride (3:7) to pure chloroform gave 0.084 g. of an oil which on the basis of its infrared spectrum and retention time on gas chromatography was probably *trans*-4,5-dimethoxycyclooctanol, formed by catalytic reduction of the unchanged cycloheptanone **6a**.

The over-all yield of the cyclooctanone **8** was 23% from the ketone **6a**. An analytical sample was prepared by distillation (block temp. up to 100°, 0.15 mm.) and had m.p. 32–33°; $[\alpha]^{30}_{578}$ + 29.44°, $[\alpha]^{30}_{546}$ +32.16°, $[\alpha]^{30}$D calculated from the preceding rotations +28.53° (*c* 5.52, chloroform); n.m.r. (CDCl₃): 6.5–7.1 (8H, two singlets superimposed on multiplet), 7.1–8.4 τ (10H, multiplet). The mass spectrum showed a molecular ion peak at m/e 186.

Anal. Calcd. for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.62; H, 9.76.

(1*S*:2*S*)-(+)-**1,2-Dimethoxycyclooctane (9). (a).**—A mixture of 0.12 g. of ketone **8**, a pellet of potassium hydroxide, 3 ml. of diethylene glycol, and 0.75 ml. of 85% hydrazine hydrate were heated at the reflux temperature for 1 hr.[20] The bath temperature was increased to 185–200° and kept at this temperature

(19) From the aqueous acidic extracts more ketone **6a** and the original ketonitrile **6b** could be obtained by extraction with methylene chloride This mixture was combined with the residue from the short-path distillation (which was mostly ketonitrile) and treated with 30% sulfuric acid as above to obtain more of the cycloheptanone **6a**.

(20) Huang-Minlon, *J. Am. Chem. Soc.*, **68**, 2487 (1946).

for 3 hr. during which time water distilled from the reaction vessel. Water (10 ml.) was added to the combined distillate and residue and the mixture was extracted with ether. The extracts were washed with dilute hydrochloric acid and water, dried, and the solvent was removed. The residue was distilled through a short-path still yielding 0.085 g. (76%) of the diether 9. An analytical sample was collected by gas chromatography. The diether had $[\alpha]^{31.8}_{578} + 52.4°$, $[\alpha]^{31.8}_{546} + 58.9°$, $[\alpha]^{31.8}$D calculated from the preceding rotations $+50.3°$ (c 4.63, chloroform).

Anal. Calcd. for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 69.55; H, 11.83.

(b).—To a stirred, ice-cooled solution of 0.067 g. of (+)-*trans*-1,2-cyclooctanediol (10) in 10 ml. of methylene chloride was added 0.18 ml. of fluoroboric acid solution (prepared by addition of 0.133 ml. of 50% fluoroboric acid to 25 ml. of 3:1 ether–methylene chloride). A solution of diazomethane in ether was added until the yellow color of diazomethane persisted. More of the catalyst solution (0.05 ml.) was added whereupon the yellow color disappeared, and more diazomethane was added as before.[21] A few drops of the catalyst solution was added to decompose the excess diazomethane. Four pellets of potassium hydroxide were added, the solution was filtered through magnesium sulfate, and the solvent was removed. The residue was distilled through a short-path still.[22] The pure diether 9 was ob-

tained from the distillate by collection from gas chromatography (silicone rubber, 90°) as a colorless oil (0.040 g., 50%). It had $[\alpha]^{31}_{578} + 51.4°$, $[\alpha]^{31}_{546} + 57.1°$, $[\alpha]^{31}$D calculated from the preceding rotations $+49.5°$ (c 4.337, chloroform).

Anal. Calcd. for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 69.81; H, 11.70.

The infrared spectra and retention times of the (+)-*trans*-1,2-dimethoxycyclooctane (9) prepared by the two methods were identical and very different from those of *cis*-1,2-dimethoxycyclooctane.

cis-1,2-Dimethoxycyclooctane was prepared by treatment of *cis*-1,2-cyclooctanediol[24] with diazomethane–fluoroboric acid in the manner described for the *trans* isomer. It displayed the following n.m.r. spectrum (CDCl₃): 6.63 (8H, singlet superimposed on broad peak), 8.4 τ (12H, broad multiplet).

Anal. Calcd. for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 69.84; H, 11.67.

(+)-*trans*-1,2-Cyclooctanediol (10) was prepared[6,25] by osmylation of (−)-*trans*-cyclooctene[5] [$[\alpha]^{28}_{578} - 432°$, $[\alpha]^{28}_{546} - 500°$, $[\alpha]^{28}$D calculated from the preceding rotations $-412°$ (c 1.110, methylene chloride)] and decomposition of the osmate ester with sodium sulfite. The glycol was obtained in 64% yield and had $[\alpha]^{31}_{578} + 17.21°$, $[\alpha]^{31}_{546} + 19.46°$, $[\alpha]^{31}$D calculated from the preceding rotations $+16.51°$ (c 3.34, absolute ethanol).

(21) The alkylation is not instantaneous and to ensure complete alkylation it was essential to add diazomethane until the yellow color persisted for about 5–10 min. The alkylation could be followed by gas chromatography (silicone rubber, 90°); a peak corresponding to monoalkylated product was seen when there was incomplete alkylation (or if the alkylation was carried out at −20°).

(22) A sample of optically inactive *trans*-1,2-dimethoxycyclooctane prepared by methylation of *trans*-1,2-cyclooctanediol²³ had b.p. 97–100° (18

mm.). *Anal.* Calcd. for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 69.64; H, 11.70.

(23) A. C. Cope, S. W. Fenton, and C. F. Spencer, *J. Am. Chem. Soc.*, **74**, 5884 (1952).

(24) *cis*-1,2-Cyclooctanediol was prepared from *cis*-cyclooctene, sodium chlorate, and osmium tetroxide.²³

(25) This reaction on the optically active olefin was first performed by Dr. T. V. Van Auken.

The Stabilities of Heteroaromatic Sulfur-Containing Cations

BY R. G. TURNBO, D. L. SULLIVAN, AND R. PETTIT

The pK_R⁺ determinations have been made for several aromatic sulfur-containing cations and a comparison of these systems with their isoelectronic homonuclear carbon cations is given. Replacement of a double bond by a sulfur atom is found to enhance considerably the stability (as measured by the electrophilicity) of the cation. A satisfactory linear relationship is found to exist between the pK_R⁺ values and the π-electron localization energies for the cations. Hückel molecular orbital calculations suggest that the reason for the increased stability of the sulfur-containing cations is the conjugate bases of these systems possess a much lower π-electron bonding energy than the carbon systems.

Introduction

Previous investigations in these laboratories into the chemistry of aromatic sulfur-containing cations have shown that the thiapyrylium (I) and thienotropylium (II) cations are more stable (less electrophilic) than the tropylium cation (III).[1,2] This order of stability is indicated by the relative
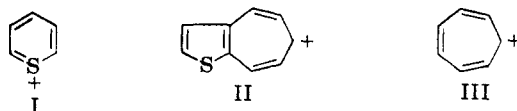
pK_R⁺ values associated with the three species and also by the fact that the tropylium cation will abstract a hydride ion from the heterocyclic compounds obtained upon treatment of the cations I and II with sodium borohydride to regenerate these cations.
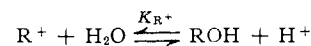
That the thienotropylium cation is more stable in this sense than the tropylium ion is especially interesting as the benztropylium cation, which is iso-

electronic with II, is considerably *less* stable than the tropylium cation.[3]

These results have then prompted the present investigation into the stability of several other aromatic sulfur-containing cations and a comparison of these with their corresponding carbocyclic analogs.

Results and Discussion

A measure of the relative electrophilicities of a series of carbonium ions is afforded by the various equilibrium constants (K_R⁺) involved in the following reaction

$$R^+ + H_2O \underset{}{\overset{K_R^+}{\rightleftharpoons}} ROH + H^+$$

The pK_R⁺ values for several thienyl cations isoelectronic with the diphenylmethyl and the triphenylmethyl carbonium ions have now been measured and are listed in Table I together with those for the thiapyrylium and thienotropylium cations. The values associated with the diphenylmethyl, triphenylmethyl, and tropylium cations are also listed for comparison.

(1) R. Pettit, *Tetrahedron Letters*, No. **23**, 11 (1960).

(2) D. Sullivan and R. Pettit, *ibid.*, No. **6**, 401 (1963).

(3) G. Naville, H. Strauss, and E. Heilbronner, *Helv. Chim. Acta*, **43**, 1221 (1960).