causing the titration of one group to begin before that of the other group has been completed. Quite satisfactory results were obtained by applying the Noyes method[10] for separation of the overlapping pK_a' values (see Table IV). Since 2-furoic acid (pK_a = 3.12[11]) is stronger than 3-furoic acid (pK_a = 3.99[11]), we attributed the determined pK_a' = 2.65 to carboxyl group in position 2, and the pK_a' = 3.96 to the carboxyl group in position 4 of the 2,4-furandicarboxylic acid.

The thermodynamic pK_a for the 3-furoic acid, 5-bromo-3-furoic acid, and 5-nitro-3-furoic acid and the stronger group of the dibasic acid were calculated from the equation

$$pK_a = pK_a' - \log \gamma_i \quad (3)$$

and using the Debye–Hückel limiting law to define the activity coefficient, γ_i, and the value of the ionic strength at the midpoint of the titration. The thermodynamic pK_a becomes pK_a' + 0.04 (see Table IV).

The thermodynamic pK_a of the weaker group of the 2,4-furandicarboxylic acid was calculated from the equation

$$pK_a = pK_a' - 3 \log \gamma_i \quad (4)$$

The activity coefficient was calculated from the equation

$$-\log \gamma_i = \frac{A\sqrt{I_m}}{1 - Ba_i\sqrt{I_m}} \quad (5)$$

Using the values of the constants A and B,[12] the value of the ionic size parameter,[13] and the value of the ionic strength of the solution, I_m, at the semineutralization, the thermodynamic pK_a becomes pK'_{a2} + 0.17 (see Table IV).

We have correlated, by multiple linear regression analysis,[14] the acidity constants values of the 5-substituted 3-furoic acids to the corresponding substituent constants values σ_m and σ_p, employing values determined by McDaniel and Brown.[15]

With the σ_m values the slope ρ of the regression line is 1.25 and the correlation coefficient is 0.983; with the σ_p values ρ is 1.28 and the correlation coefficient is 0.990. It is noteworthy that 5-substituted 3-furoic acids correlate well with both meta and para substituent constants.

The ratio between the value of ρ obtained and the corresponding values for the benzene system agrees with those found for the 2-R-5-Y system[2,16] and reinforces the conclusion that the transmission of the substituent's effect is greater in the furan ring than in the benzene ring.

Supplementary Material Available. Tables II and III that report full determination of the apparent acidity constant data for the 5-substituted 3-furoic acids (2 pages). Ordering information is given on any current masthead page.

References and Notes

(1) Supported in part by the Fundação de Amparo à Pesquisa do Estado de São Paulo.
(2) H. H. Jaffé and H. L. Jones, *Adv. Heterocycl. Chem.*, **3**, 209 (1964).
(3) R. H. Wiley and N. R. Smith, *Org. Synth.*, **31**, 23 (1951).
(4) J. Fried and R. C. Erdelfield, *J. Org. Chem.*, **6**, 577 (1941).
(5) R. H. Wiley and I. H. Knabeschuh, *J. Am. Chem. Soc.*, **77**, 1615 (1955).
(6) H. Gilman and R. Burtner, *J. Am. Chem. Soc.*, **65**, 2903 (1933).
(7) T. Reichstein and H. Zschokke, *Helv. Chim. Acta*, **15**, 268 (1932).
(8) L. F. Fieser, "Organic Experiments", D. C. Heath, Boston, Mass., 1966, p 68.
(9) A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases", McThuen, London, 1962, p 16.
(10) A. A. Noyes, *Z. Phys. Chem. (Leipzig)*, **11**, 495 (1893); cf. H. T. S. Britton, "Hydrogen Ions", Chapman and Hall, London, 1955.
(11) Y. Osuji, M. Kubo, and E. Imoto, *Nippon Kagaku Zasshi*, **80**, 1300 (1959).
(12) J. N. Butler, "Ionic Equilibrium—A Mathematical Approach", Addison-Wesley, Reading, Mass., 1964, p 433.
(13) J. Kielland, *J. Am. Chem. Soc.*, **59**, 1675 (1937).
(14) H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953).
(15) D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, **23**, 420 (1968).
(16) W. K. Dwok, R. A. More O'Ferrall, and S. I. Miller, *Tetrahedron*, **20**, 1913 (1964).
(17) W. E. Catlin, *Iowa State Coll. J. Sci.*, **10**, 65 (1935).

A Convenient Synthesis of *N-tert*-Butyloxycarbonyl-*O*-benzyl-L-serine

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In peptide synthesis, especially using the solid-phase method, *N-tert*-butyloxycarbonyl-*O*-benzyl-L-serine has proved to be a useful intermediate to incorporate serine into a synthetic peptide.[1] Although several methods are currently available for the preparation of the *O*-benzyl derivative, they are laborious and not profitable for commercial exploitation. *O*-Benzyl-DL-serine was prepared by Okawa[2] via bromination of methyl acrylate. Resolution into the L isomer was achieved by hydrolysis of the *N*-acetyl derivative with the acylase.[3] In addition, *N-tert*-butyloxycarbonyl-*O*-benzyl-L-serine was prepared by Hruby and Ehler[4] via benzylation of *N-tert*-butyloxycarbonyl-L-serine in sodium–liquid ammonia at −30 °C. Isolation of the desired product was performed by use of column chromatography. This paper is concerned with the development of a more convenient synthetic method starting from L-serine.

N-tert-Butyloxycarbonyl-*O*-benzyl-L-serine was obtained directly from the readily available *N-tert*-butyloxycarbonyl-L-serine by treatment of the latter compound, in dimethylformamide at room temperature, with 2 molar equiv of sodium hydride and 1 molar equiv of benzyl bromide. Purified *N-tert*-butyloxycarbonyl-*O*-benzyl-L-serine was obtained in 57% yield as its cyclohexylammonium salt after recrystallization from ethyl acetate. The method described here is suitable for large-scale preparation because of its high efficiency, procedural simplicity, and mildness of reaction conditions.

When the same procedure was applied to the preparation of the *O*-benzyl-L-threonine derivative, the yield of the compound was low as revealed by thin layer chromatography. By use of column chromatography *N-tert*-butyloxycarbonyl-*O*-benzyl-L-threonine was isolated in 14% yield.

Experimental Section[5]

***N-tert*-Butyloxycarbonyl-*O*-benzyl-L-serine Cyclohexylammonium salt.** To a solution of *N-tert*-butyloxycarbonyl-L-serine[6] (2.05 g, 10 mmol) in dimethylformamide (50 ml) was added sodium hydride (65%) (820 mg, 22 mmol) at 0 °C. After the evolution of hydrogen gas ceased, the freshly distilled benzyl bromide (1.88 g, 11 mmol) was added to the solution. The reaction mixture was stirred at 25–30 °C for 5 h to give a clear solution. The solvent was then removed under reduced pressure below 40 °C. The residue was dissolved in water (50 ml) and the solution was extracted with ether (two 20-ml portions). The aqueous phase was acidified to pH 3.5 with 3 N HCl, and extracted with ethyl acetate (five 20-ml portions). The combined organic layers were washed with water and dried over magnesium sulfate. The ethyl acetate was removed under reduced pressure to give a colorless oil. The oil was then dissolved in ether (30 ml) and cyclohexylamine (0.9 g) was added to the solution. A precipitate formed and was collected by filtration. The solid was washed well with ether. Recrystallization from ethyl acetate yielded the title compound (2.2 g, 57%): mp 159–160 °C; $[\alpha]^{25}D$ +29.0° (*c* 1, methanol) [authentic sample prepared by the known method,[6] mp 159–160 °C; $[\alpha]^{25}D$ +29.8° (*c* 1, methanol)].

Anal. Calcd for $C_{15}H_{21}NO_5 \cdot C_6H_{13}N$: C, 63.93; H, 8.69; N, 7.10. Found: C, 63.76; H, 8.54; N, 6.89.

Optical Purity of *O*-Benzyl-L-serine. One gram of *N-tert*-butyloxycarbonyl-*O*-benzyl-L-serine prepared by the above procedure was dissolved in 2 N HCl–AcOH (5 ml). After 1 h at room temperature, the solvent was evaporated under reduced pressure below 35 °C to yield crystals. The crystals showed the same optical rotations as a sample of *O*-benzyl-L-serine hydrochloride prepared by the method previously reported,[3] $[\alpha]^{25}D$ +7.4° (*c* 2, 1 N HCl).

Registry No.—*N-tert*-Butyloxycarbonyl-*O*-benzyl-L-serine cyclohexylammonium salt, 30200-52-3; *N-tert*-butyloxycarbonyl-L-serine, 3262-72-4; benzyl bromide, 100-39-0; *N-tert*-butyloxycarbonyl-*O*-benzyl-L-serine, 23680-31-1.

References and Notes

(1) R. B. Merrifield, *Adv. Enzymol. Relat. Areas Mol. Biol.*, **32**, 221 (1969).
(2) K. Okawa and H. Tani, *J. Chem. Soc. Jpn.*, **75**, 1197 (1950); K. Okawa, *Bull. Chem. Soc. Jpn.*, **30**, 110 (1957).
(3) K. Okawa, *Bull. Chem. Soc. Jpn.*, **29**, 486 (1956).
(4) V. J. Hruby and K. W. Ehler, *J. Org. Chem.*, **35**, 1690 (1970).
(5) All melting points are uncorrected. Thin layer chromatography was performed on silica gel plates (Merck) using chloroform–methanol–acetic acid (95:5:3).
(6) H. Otsuka, K. Inouye, F. Shinozaki, and M. Kanayama, *Bull. Chem. Soc. Jpn.*, **39**, 1171 (1966).

A Novel Reaction of Sulfur Trioxide with Fluoro Olefins

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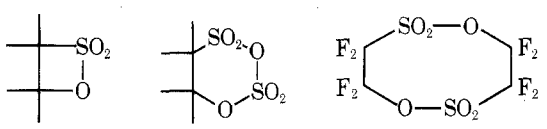
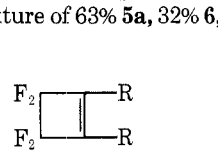
It is well known that sulfur trioxide reacts with fluoro olefins to normally give stable β-sultones (**1**) and β-disultones (**2**).[1] Tetrafluoroethylene is reported to also give the unusual eight-membered ring heterocycle **3**. In some cases, the β-sultone products rearrange to alkenyl fluorosulfates (–C=C–OSO_2F) under the reaction conditions. Polyfluorocyclobutenes are reported here to react in a novel manner with sulfur trioxide to give a new class of products, 3-(fluorosulfato)polyfluorocyclobutenes.

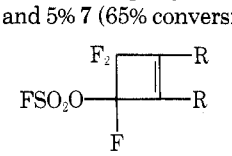


1 **2** **3**

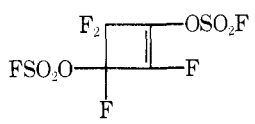
Hexafluorocyclobutene (**4a**) reacts slowly with sulfur trioxide at room temperature and reacts rapidly at 100 °C to give a mixture of 63% **5a**, 32% **6**, and 5% **7** (65% conversion, 91% yield). At 100 °C, **4a** reacts with 2 equiv of sulfur trioxide to give 34% **5a**, 50% **6**, and 16% **7**. Similarly at 100 °C, **4b** gives **5b**. 3,3,4,4-Tetrafluorocyclobutene (**4c**) reacts exothermally with sulfur trioxide at room temperature to give **5c** in 74% yield. There are no appreciable sultone products or 1-cycloalkenyl fluorosulfate monoadducts detected in these reactions.



4a, R = F
b, R = Cl
c, R = H



5a, R = F
b, R = Cl
c, R = H



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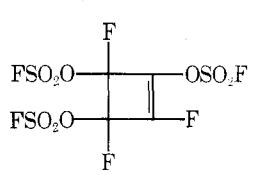

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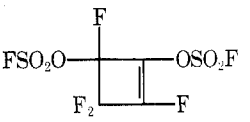
In contrast with **4a** and **4b**, the acyclic analogue octafluoro-2-butene, $CF_3CF{=}CFCF_3$, does not react appreciably with sulfur trioxide at 100 °C,[2] and 2,3-dichlorohexafluoro-2-butene, $CF_3CCl{=}CClCF_3$, is reported to give the β-sultone.[3]

The structures of the reaction products are readily established by ir and NMR analyses. The comparable carbon–carbon double bond vibrational stretching frequencies in **4a–c** and **5a–c** confirm the double bond substitution pattern: **5a** (1792 cm^{-1}), **4a** (1799 cm^{-1}), **5b** (1629 cm^{-1}), **4b** (1620 cm^{-1}), **5c** (1561 cm^{-1}), **4c** (1560 cm^{-1}). The double bond stretching frequencies in **6** and **7** appear at 1762 and 1765 cm^{-1}, respectively, which are comparable to the stretching frequency in 1-methoxypentafluorocyclobutene (1765 cm^{-1}). The NMR spectra of **5a–c** are also consistent with the assigned structures (see Experimental Section).

For the 2:1 adduct, it is not obvious whether **6** or **8** is the correct structure. The NMR spectrum of this adduct was



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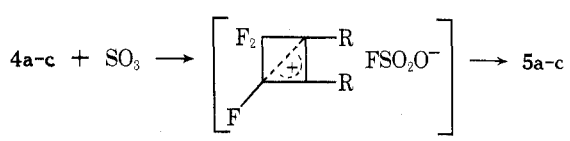
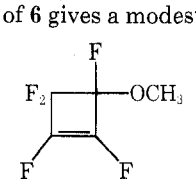
analyzed with computer assistance to obtain the F–F couplings (see Experimental Section). The vinyl fluorine cross couples with the nonequivalent geminal fluorines by 14.4 and 15.2 Hz, while it couples with an adjacent fluorine by 4.4 Hz. When compared with model fluorinated cyclobutenes, the observed couplings are consistent only with structure **6**.[4]

The initial step in the reaction of sulfur trioxide with olefins is normally an electrophilic attack by sulfur trioxide on the double bond to give an intermediate π complex which rearranges to a zwitterionic intermediate (^+C–C–OSO_2^-). Depending upon the fluoro olefin and the reaction conditions, this intermediate usually collapses directly to β-sultone product (**1**) or reacts with an additional 1 equiv of sulfur trioxide, followed by collapse to β-disultone (**2**). For the cyclobutenes **4a–c**, a competitive pathway which involves sulfur trioxide attack on an allylic fluorine to generate an intermediate cyclobutenyl fluorosulfate ion pair is suggested.



In contrast with acyclic alkenyl cations where charge is delocalized only by classical allyl resonance, cyclobutenyl cations can be further stabilized by 1,3-π overlap.[5] This may in part contribute to the increased reactivity of **4a** over its acyclic analogue, octafluoro-2-butene. Similarly, the potential allyl cation generated by attack of sulfur trioxide on an allylic fluorine in 2,3-dichlorohexafluoro-2-butene is less stable than the corresponding cyclobutenyl cation generated from **4b**; therefore, sulfur trioxide preferentially adds to the double bond in the acyclic alkene to give normal β-sultone product.

The cyclobutenyl fluorosulfates **5** are useful alkylating agents. For example, methanolysis of **5a** gives **9** in 80% yield, the only known practical route to this compound.[6] Methanolysis of **6** gives a modest yield (40%) of **10**.



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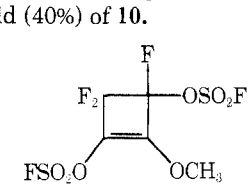

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Experimental Section

All NMR spectra were recorded on a Varian Associates XL-100 spectrometer. The ^1H NMR spectra are referenced to internal tetramethylsilane and the ^{19}F NMR spectra are referenced to internal