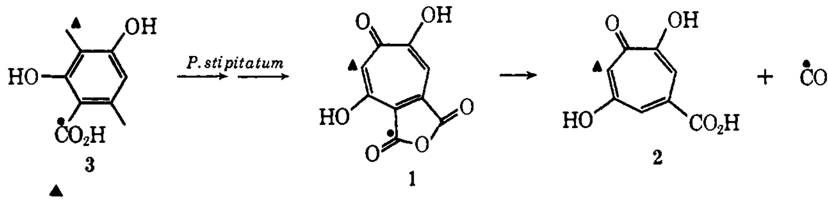
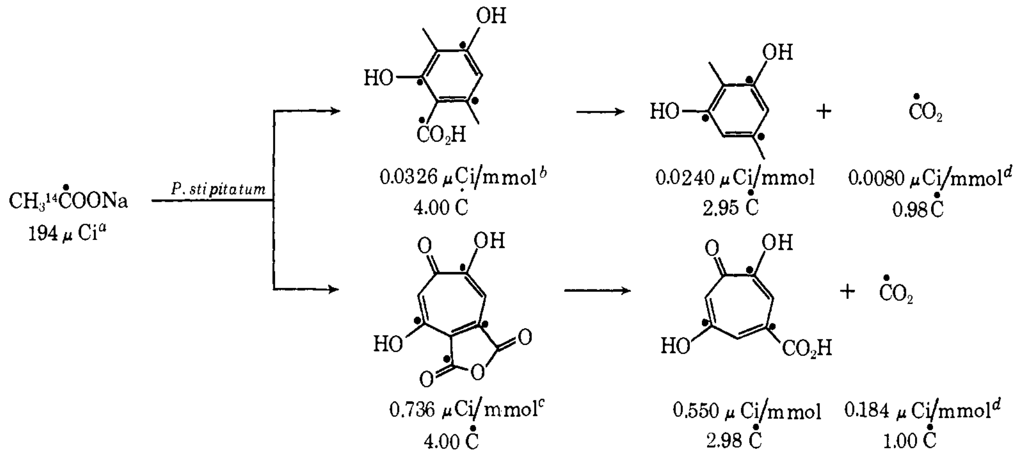
Scheme II



3	1	2	CO_2
$\overset{\blacktriangle}{}$ $3\text{-}^{14}CH_3\text{-}3\text{-}MOA$[a] 12.7 μCi fed[b]	0.123 μCi/mmol[c] 1.00 $\overset{\blacktriangle}{C}$	0.121 μCi/mmol 0.98 $\overset{\blacktriangle}{C}$	0.005 μCi/mmol[d] 0.04 $\overset{\blacktriangle}{C}$
$\overset{\bullet}{}$ $1\text{-}^{14}COOH\text{-}3\text{-}MOA$ 5.4 μCi fed[b]	0.151 μCi/mmol[c] 1.00 $\overset{\bullet}{C}$	0.005 μCi/mmol 0.03 $\overset{\bullet}{C}$	0.137 μCi/mmol[d] 0.91 $\overset{\bullet}{C}$

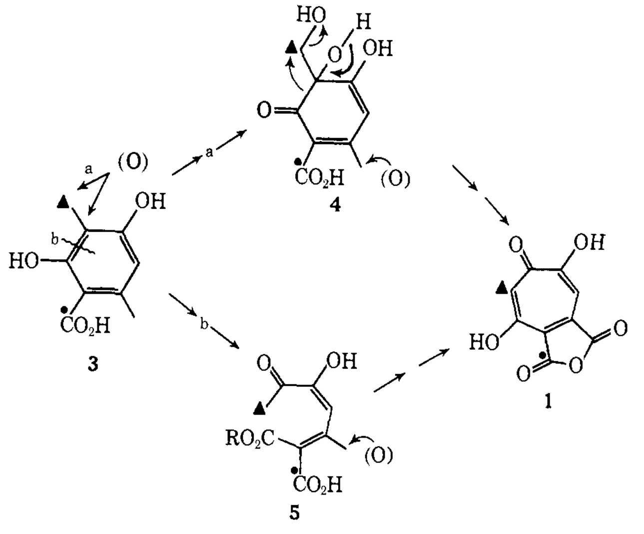
[a] 3-MOA = 3-methylorsellinic acid. [b] Two 350-ml cultures. [c] From 14-day old culture media. [d] As $BaCO_3$.

Scheme III



[a] Two 350-ml cultures. [b] The crude 3-MOA isolated from the 11-day old culture media with carrier 3-MOA had a radioactivity of 1.09 μCi/mmol and was diluted again with authentic 3-MOA. [c] The isolated and purified stipitatonic acid had a radioactivity of 9.56 μCi/mmol and was diluted with authentic stipitatonic acid. [d] As $BaCO_3$.

Scheme IV



results. Experiments to distinguish between the *oxygenase*-ring expansion route *via* **4** (Scheme IV, path a) and the *dioxygenase*-recyclization process *via* **5** (Scheme IV, path b) are in progress using $^{18}O_2$.

Acknowledgment. Support of this investigation by a NIH grant (AI 08920) is gratefully acknowledged.

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Polar Effects upon Free Radicals. Stereoselectivity in the Kochi Reaction

Sir:

Formation of alkyl halides from carboxylic acids by decarboxylation with lead tetraacetate and halide salt has been described by Kochi.[1] The reaction is especially useful in the synthesis of alkyl chlorides.[1,2] The stereochemistry of the reaction is consistent with a free-radical chain mechanism.[1-3] We wish to report that the Kochi reaction is also useful in demonstrating substantial polar effects of remote substituents upon free-radical stereoselectivities in chlorine atom transfer.

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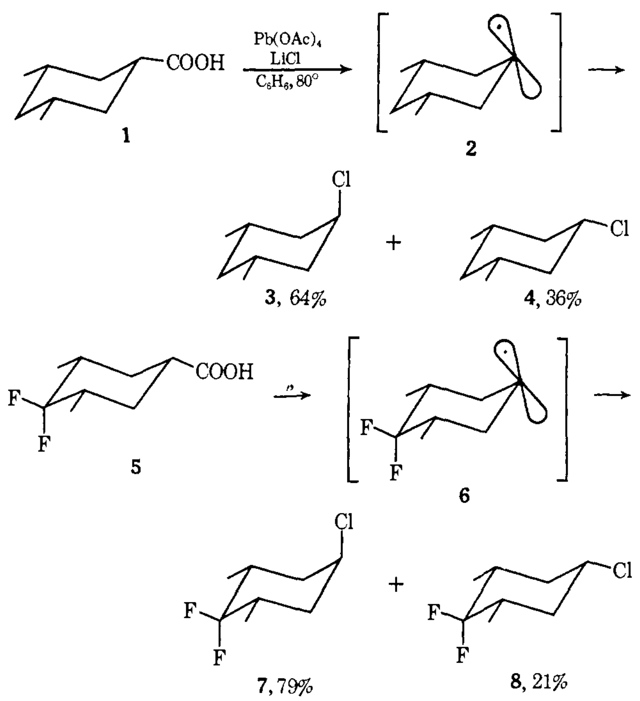
(1) J. K. Kochi, *J. Amer. Chem. Soc.*, 87, 2500 (1965); *J. Org. Chem.*, 30, 3265 (1965).

(2) R. D. Stolow and T. W. Giants, *Tetrahedron Lett.*, 695 (1971).

(3) P. D. Bartlett, G. N. Fickes, F. C. Haupt, and R. Helgeson, *Accounts Chem. Res.*, 3, 177 (1970).

When acids **1** and **5** are subjected to the Kochi reaction with lead tetraacetate and lithium chloride in benzene solution at 80° under identical conditions, their axial–equatorial chloride product ratios differ significantly: (**3**)/(**4**) = 1.8, (**7**)/(**8**) = 3.8. Since the two intermediate radicals (**2** and **6**) differ only at the remote C-4 position, steric effects in the vicinity of C-1 in the chlorine atom transfer step of the Kochi reaction should be essentially the same for radicals **2** and **6**.[4] Therefore, the major factor responsible for the product ratio differences [(**3**)/(**4**) $\neq$ (**7**)/(**8**)] would appear to be a polar effect involving the *gem*-fluoro group of radical **6**.



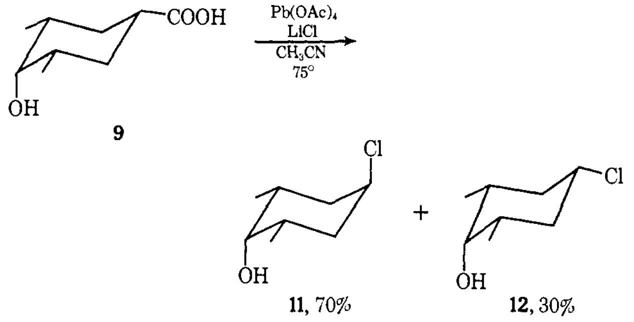
In the chlorine atom transfer step, an electron attracting transannular substituent (the *gem*-fluoro group in radical **6**) stabilizes the transition state leading to axial chlorine (**7**) relative to the competing transition state leading to equatorial chlorine (**8**). The observed product ratios show that the two competing chlorine atom transfer transition states differ by 430 cal/mol for radical **2** and by 930 cal/mol for radical **6**. Thus, the polar effect of the *gem*-fluoro group (CF_2) relative to the nonpolar methylene group (CH_2) stabilizes the axial transition state relative to the equatorial transition state by a substantial amount, 500 cal/mol.[5]

The magnitude and direction of the polar effect should depend upon geometry and charge distribution in the competing transition states for chlorine atom transfer, and may be useful in elucidating transition state structure. Reactions with similar free-radical mechanisms should show similar polar effects. For example, we would predict similar results in chlorine atom transfer if radicals **2** and **6** were generated from hypochlorites[3,9] or mercuric chlorides.[4] It is reasonable to expect that where bonding between elements of substantially different electronegativity occurs in a radical reaction, transition state energies may be influenced significantly by polar effects.[10] Comparison of radicals like **2** and **6** should have broad applicability as a diagnostic tool in free-radical chemistry.

Reaction of *cis,cis*-3,5-dimethylcyclohexanecarboxylic acid[11] (**1**), mp 69–70.5°, gave *trans,trans*-3,5-dimethylcyclohexyl chloride[12] (**3**) with chlorine axial, plus its cis,cis epimer[12] (**4**) with chlorine equatorial in 60% yield. The isomer ratio, (**3**)/(**4**), was determined by gas chromatography and confirmed by integration of the C-1 proton nmr signals of **3** and **4** in the product mixture.[13]

Reaction of 4,4-difluoro-*cis,cis*-3,5-dimethylcyclohexanecarboxylic acid (**5**), mp 78–80°, gave chlorides **7** and **8** in 60% total yield. The isomer ratio, (**7**)/(**8**), was determined by gas chromatography and confirmed by nmr.

cis,cis-3,5-Dimethyl-*cis*-4-hydroxycyclohexanecarboxylic acid (**9**), mp 115–116°, and *cis,cis*-3,5-dimethyl-4-oxocyclohexanecarboxylic acid (**10**), mp 132–134°, gave Kochi reaction axial–equatorial product ratios between the extremes of acids **1** and **5**. The methyl ester of **10**, mp 42–43°, with sulfur tetrafluoride,[14] gave the methyl ester of **5**, 76%, bp 92° (5 mm), which upon hydrolysis, yielded acid **5** (J_{FCF} = 239 Hz).



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[4] Steric effects upon halogen atom transfer to a cyclohexyl free radical have been discussed in detail. See F. R. Jensen, L. H. Gale, and J. E. Rodgers, *J. Amer. Chem. Soc.*, **90**, 5793 (1968), and references cited.

[5] $\Delta\Delta G_6^{\ddagger} - \Delta\Delta G_2^{\ddagger} = 930 - 430 = 500$ cal/mol. Substantial polar effects apparently have not been demonstrated previously for chlorine atom transfer to 4-substituted cyclohexyl free radicals. Russell, *et al.*,[6] reported that photochlorination of chlorocyclohexane in carbon tetrachloride solution at 40° gave *cis*-1,4- and *trans*-1,4-dichlorocyclohexane in the ratio, *cis*/*trans* = 0.9. Little, *et al.*,[7] reported that photochlorination of cyclohexanecarboxylic acid in chlorobenzene solution at 80° gave *cis*- and *trans*-4-chlorocyclohexanecarboxylic acid (*cis*/*trans* = 1.4). Price, *et al.*,[8] reported that free-radical chlorination of methyl cyclohexanecarboxylate with sulfuryl chloride and dibenzoyl peroxide in carbon tetrachloride at 70° gave methyl *cis*- and *trans*-4-chlorocyclohexanecarboxylate (cis/trans = 1.0). Interpretation of these results[6–8] is complicated somewhat because the radical intermediates would exist as conformational mixtures, and because analysis of the products was difficult.[7,8] The difference between 1.4 and 1.0 may not be real. The reported cis/trans ratios of 0.9–1.4 do not appear to support a significant polar effect in these chlorine atom transfers.[6–8] Unfortunately, 2- and 3-substituted cyclohexyl free radicals may suffer steric as well as polar effects, making interpretation of their stereoselectivities much more complex than for 4-substituted radicals.[6–8]

[6] G. A. Russell, A. Ito, and R. Konaka, *J. Amer. Chem. Soc.*, **85**, 2988 (1963). Also see D. S. Ashton and J. M. Tedder, *J. Chem. Soc. B*, 1031 (1970).

[7] J. C. Little, A. R. Sexton, Y.-L. C. Tong, and T. E. Zurawic, *J. Amer. Chem. Soc.*, **91**, 7098 (1969).

[8] C. C. Price, C. D. Beard, and K. Akune, *ibid.*, **92**, 5916 (1970).

[9] F. D. Greene, C. Chu, and J. Walia, *ibid.*, **84**, 2463 (1962); *J. Org. Chem.*, **29**, 1285 (1964).

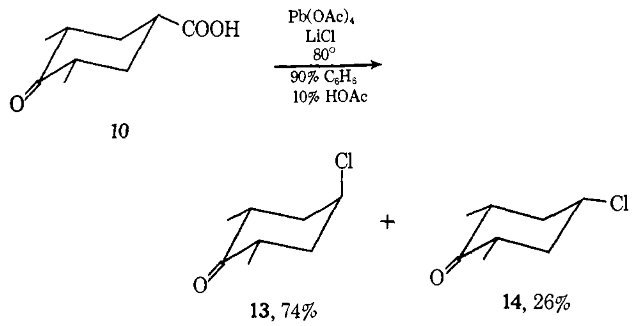
[10] W. A. Pryor, "Free Radicals," McGraw-Hill, New York, N. Y., 1966, pp 13–17, 170–176.

[11] H. van Bekkum, P. E. Verkade, and B. M. Wepster, *Koninkl. Ned. Akad. Wetenschap, Proc. Ser. B*, **64**, 161 (1961).

[12] Sh. G. Sadykhov, S. D. Mekhtiev, V. A. Soldatova, M. A. Salimov, F. A. Mamedov, and N. S. Guseinov, *Neftekhimiya*, **8**, 655 (1968).

[13] The downfield C-1 proton signal, a quintet of band width 11.4 Hz, was assigned to **3** (C-1 proton equatorial). The upfield C-1 proton signal, a triplet of triplets of band width 31.1 Hz, was assigned to **4** (C-1 proton axial). Percentages given under the drawings show the composition of the product mixtures.

[14] W. R. Hasek, W. C. Smith, and V. A. Engelhardt, *J. Amer. Chem. Soc.*, **82**, 543 (1960).



Jones oxidations[15] of chloro alcohols to chloro ketones and conversions of chloro ketones with sulfur tetrafluoride[14] into chlorodifluorides were stereospecific, so that independent product syntheses **11** → **13** → **7** and **12** → **14** → **8** proceeded in good yield without detectible epimerization.

Acknowledgment. We wish to thank the National Science Foundation, the Research Corporation, and an anonymous donor for support of this work. The 100-MHz nmr spectrometer was purchased with the aid of matching funds from National Science Foundation Grant No. GP-8171.

(15) J. Meinwald, J. Crandall, and W. E. Hymans, *Org. Syn.*, **45**, 77 (1965); R. G. Curtis, I. Heilbron, E. R. H. Jones, and G. F. Woods, *J. Chem. Soc.*, 457 (1953).

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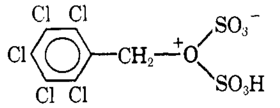
Selective Oxidations by Sulfur Trioxide

Sir:

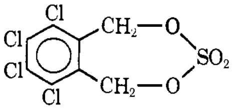
Although it has been recognized for some time that sulfur trioxide is a powerful oxidant, its use as such for organic compounds has not so far been developed. The main reason for not utilizing its oxidizing properties was the indiscriminate reaction pattern it exhibited when it was contacted with a variety of substrates, mainly hydrocarbons. With paraffins and olefins, it gave messy, intractable reaction mixtures due to the intermeshing of various, not fully clarified oxidation, rearrangement, condensation, polymerization, sulfonation, and sulfation reactions, the complex nature of which apparently discouraged the consideration of sulfur trioxide as a manageable oxidizing agent. In contrast, its use as a sulfonating agent for unsaturated compounds and as a sulfating agent for alcohols is well developed and amply documented.[1]

We now wish to demonstrate that sulfur trioxide can be of considerable synthetic value as an oxidant when used with the proper reaction partners. These are organic compounds in which some parts of the molecule are protected by appropriate substitution while others remain susceptible to oxidation by sulfur trioxide. The reaction of 2,3,4,5,6-pentachlorotoluene (**1**) provides a representative example.

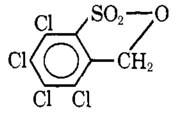
When 26.4 g (0.1 mol) of **1**[2a] was added in one portion to an excess (200 ml) of liquid (stabilized) sulfur trioxide (**2**), and the resultant mixture was refluxed with good stirring, an intensely blue color developed, accompanied with the evolution of sulfur dioxide, which continued for 2–3 hr and amounted to 0.1 mol. After removal of excess **2**, 45.2 g of a greenish gray solid, **3**, with the composition of $C_7H_3Cl_5O_7S_2$ was recovered. The latter, on addition to water, followed by heating of the resultant aqueous slurry to reflux, precipitated 26.6 g of a white, powdery material which after dissolution in acetic acid[3] and reprecipitation yielded 24.5 g (91%) of 2,3,4,5,6-pentachlorobenzyl alcohol (**4**), mp 195.0–196.5°. When **3** was added directly to aqueous sodium hydroxide or ammonium hydroxide solutions, the corresponding salts of the hydrogen sulfate ester of **4** were obtained. These data and reactions suggest that **3** is the hydrogen sulfate ester of **4** solvated by 1 mol of **2** as shown in structure A. This was confirmed by its nmr spectrum, run in **2** at the end of the heating period, which showed that the proton peak of **1** at δ 2.52 had completely disappeared and that two new peaks at δ 6.29 and 9.2 were present in a 2:1 ratio.[4] The former corresponds to the two benzylic hydrogens and the latter to the acidic proton of the sulfuric acid moiety in A.[5-7] In corroboration of structure A, **3** was prepared also from **4** and **2**.



A



B



C

The oxidation reaction illustrated with **1** was found to be of a rather wide scope and includes not only chlorinated, fluorinated, and brominated toluenes, but the halogenated xylenes and higher methylbenzenes as well. For instance, the reaction of tetrachloro or tetrabromo *m*- and *p*-xylenes provides a convenient, one-step preparation of the corresponding xylylene diols.[8] These reactions seem to be characteristic of the methyl side chains, since *ar*-pentachloroethylbenzene yields *ar*-pentachloro-β-*trans*-styrenesulfonic acid and *ar*-pentachlorocumene forms *ar*-pentachlorobenzenesulfonic acid. When the aromatic nuclei are not fully protected by substitution, sulfonation may accompany the oxidation reaction. With hydrogens in

(1) E. E. Gilbert, "Sulfonation and Related Reactions," Interscience, New York, N. Y., 1965.

(2) (a) P. G. Harvey, F. Smith, M. Stacey, and J. C. Tatlow, *J. Appl. Chem.*, 4, 325 (1954); (b) S. D. Ross and M Markarian, *J. Amer. Chem. Soc.*, 71, 2756 (1949).

(3) The small amount of material insoluble in acetic acid was identified as *ar*-decachlorodibenzyl ether, mp 223–225°, and a mixture of *ar*-decachlorodiphenylmethane and isomeric *ar*-nonachlorophenyltolylmethanes. *ar*-Pentafluorotoluene yielded a somewhat higher proportion of alkylation products.

(4) The chemical shift of the low-field peak is somewhat variable during the reaction between δ 9.2 and 9.6.

(5) The chemical shift of the benzylic protons at δ 6.29 of **3** is at an intermediate position between that of hydrogen sulfate ester of **4** (δ 5.05 in DMSO) and those of the benzylic cations (*e.g.*, pentamethylbenzyl cation at δ 8.66 in SbF_5–SO_2 solution[6]).

(6) J. M. Bollinger, M. B. Comisarow, C. A. Cupas, and G. A. Olah, *J. Amer. Chem. Soc.*, **89**, 5687 (1967).

(7) The preferred *Chemical Abstracts* name of A is pentachlorobenzyldisulfooxonium hydroxide inner salt: Dr. K. L. Loening, Chemical Abstracts Service, personal communication.

(8) Tetrahalo-*o*-xylenes give predominantly the corresponding cyclic sulfates as the hydrolysis product, *e.g.*, B.