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Inverse Effects of Alkyl Substitution on Three-Electron S_N2 Reactions[†]

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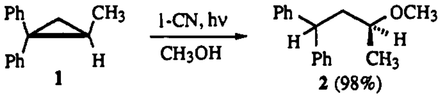
The effects of alkyl substitution on the rates of bimolecular nucleophilic substitution (S_N2) reactions at carbon serve as archetypal examples of steric effects in organic chemistry. The large rate reductions for S_N2 reactions at tertiary and neopentyl carbon atoms, for example, are cited in even the most elementary organic textbooks. In this communication, we describe several examples of three-electron S_N2 reactions that exhibit greatly diminished steric effects and occur with preferential substitution at the more hindered carbon atom, even when it is tertiary or neopentyl.

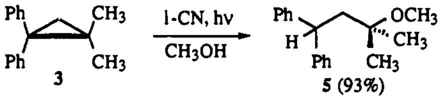
Previous experiments showed that the 1-cyanonaphthalene-sensitized (1-CN) photooxidation of optically active 1,1-diphenyl-2-methylcyclopropane (**1**) in the presence of methanol leads exclusively to ether **2**.[2] This result was rationalized by $1^{\bullet+}$ undergoing nucleophilic substitution by methanol with inversion of configuration at C2. The rate of this reaction shows second-order kinetics. These results provide compelling evidence for ring-opening by a three-electron S_N2 substitution at C2. However, the regiochemistry of the substitution was puzzling: the product of substitution at the least hindered carbon (C3) was prepared and could not be detected. The preferential addition of methanol to $1^{\bullet+}$ at C2 rather than C3 provided preliminary evidence that the effects of alkyl substitution on the regiochemistry of three-electron S_N2 reactions might be different from those of four-electron S_N2 reactions. We decided to provide more stringent tests of this hypothesis by examining the regiochemistries of methanol substitution on the cation radicals of 1,1-diphenyl-2,2-dimethylcyclopropane (**3**) and 1,1-diphenyl-2-*tert*-butylcyclopropane (**4**),[3] where tertiary and neopentyl substitutions must compete with primary substitutions.



1

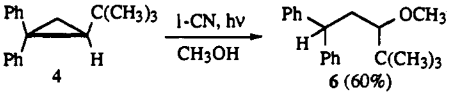
2 (98%)

Remarkably, the 1-cyanonaphthalene-sensitized photooxidation of **3** and racemic **4** in degassed methanol provided ethers **5** and **6** as the exclusive methanol substitution products.[4] The corresponding products of methanol substitution at C3 were not detected (<1%) in the reaction mixtures. These reactions are rare examples of highly selective tertiary and neopentyl nucleophilic substitutions.[5]



3

5 (93%)



4

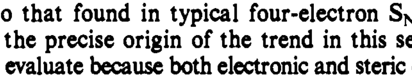
6 (60%)

Table I. Rate Constants for the Reaction of Methanol with Various 1,1-Diphenyl-2-alkylcyclopropane Cation Radicals in Dichloromethane at 22 °C[a]

substituents at C2		k ($M^{-1}\ s^{-1}$)[b]	k_{rel}
Me	H	$1.5(1) \times 10^8$	31
Et	H	$8.3(4) \times 10^7$	17
Pr^i	H	$3.0(1) \times 10^7$	6.3
Bu^t	H	$4.8(2) \times 10^6$	1
H	H	$1.7(2) \times 10^7$[c]	1
Me	H	$1.5(1) \times 10^8$	8.8
Me	Me	$3.2(1) \times 10^8$	19

[a] Product studies show that all of the alkyl-substituted cyclopropanes add methanol at C2. [b] The standard deviation in the last digit is given in parentheses. [c] Statistically corrected ($k_{obs}/2$).

The regiochemistries of methanol addition to **3** and **4** suggest that steric effects are quite small in these reactions. We tested this hypothesis by directly evaluating the steric effects. This was done by measuring the rate constants for reaction of methanol with the cation radicals shown below. These experiments attempt to keep the "electronic" effect of the substituents as constant as possible while varying their steric contributions. The cation radicals were generated by using nanosecond pulsed-laser techniques as previously described.[6] Methanol reacted with all of the cation radicals with second-order kinetics, thus providing direct evidence that the substitutions occur by an S_N2 rather than an S_N1 mechanism. The rate constants for reaction with methanol were obtained from plots of the pseudo-first-order decay rate constants vs [MeOH] (see Table I). These data reveal steric effects much smaller than those found in most four-electron S_N2 reactions. For example, the Me/Bu^t ratio in the three-electron S_N2 reaction is only 31, whereas in typical four-electron substitutions it is ca. 10^5.[7]



R = Me, Et, Pr^i, Bu^t

The rate constants for reaction of 1,1-diphenylcyclopropane cation radical ($7^{\bullet+}$) and $3^{\bullet+}$ with methanol were similarly measured by pulsed laser photolysis (see Table I). These reactions allowed the effects of mono- and dimethyl substitution at C2 to be determined by comparing the reactivities of $7^{\bullet+}$, $1^{\bullet+}$, and $3^{\bullet+}$. Interestingly, these experiments reveal that the substitution rate constants increase with increasing alkyl substitution, a trend opposite to that found in typical four-electron S_N2 reactions. Although the precise origin of the trend in this series is more difficult to evaluate because both electronic and steric contributions are changing, it is clear that steric effects do not dominate the rates of three-electron S_N2 reactions, as they do in four-electron S_N2 reactions.

The small steric effects in the three-electron S_N2 reactions can be most readily explained by Hammond's postulate.[8] On the basis

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[†] Dedicated to the memory of Professor Gerhard L. Closs, a pioneer in ion radical chemistry.

(1) Fellow of the Alfred P. Sloan Foundation, 1988-1992; recipient of an A. C. Cope Scholar Award, 1992.

(2) Dinnocenzo, J. P.; Todd, W. P.; Simpson, T. R.; Gould, I. R. *J. Am. Chem. Soc.* **1990**, *112*, 2462.

(3) The cyclopropanes were prepared: Baron, W. J.; Hendrick, M. E.; Jones, M., Jr. *J. Am. Chem. Soc.* **1973**, *95*, 6286.

(4) Preparative photolyses (Rayonet reactor equipped with 300-nm lamps) were carried out in degassed methanol with ca. 0.05 M cyclopropane and 25-35 mol % 1-cyanonaphthalene. In addition to **6**, two minor, nonsubstitution products were also obtained from **4**. These will be described in a full publication.

(5) Substitution at the more hindered carbon has also been observed for the ring-opening of some epoxides. (a) Winstein, S.; Henderson, R. B. In *Heterocyclic Compounds*; Elderfield, R. C., Ed.; Wiley: New York, 1950; Vol. 1. (b) Eliel, E. L. In *Steric Effects in Organic Chemistry*; Newman, M. S., Ed.; Wiley: New York, 1956; Chapter 2. (c) Gritter, R. J. In *The Chemistry of the Ether Linkage*; Patai, S., Ed.; Interscience: New York, 1957; p 381. (d) Parker, R. E.; Isaacs, N. S. *Chem. Rev.* **1959**, *59*, 737. (e) Rosowshy, A. In *Heterocyclic Compounds with Three- and Four-Membered Rings*; Weissberger, A., Ed.; Interscience: New York, 1964; Part 1. (f) Dittus, G. *Methoden der Organishen Chemie* (*Houben-Weyl*), 4th ed.; Verlag: Stuttgart, 1965; Vol. 6/3, p 367.

(6) (a) Reference 1. (b) Pulsed laser (308 nm, 15 ns) experiments were done using *N*-methylquinolinium hexafluorophosphate as a photosensitizer and *m*-xylene (0.2 M) as a cosensitizer. The use of positively charged sensitizers to generate cation radicals with high quantum yields in low-polarity solvents is described: Dinnocenzo, J. P.; Farid, S.; Goodman, J. L.; Gould, I. R.; Todd, W. P.; Mattes, S. L. *J. Am. Chem. Soc.* **1989**, *111*, 8973.

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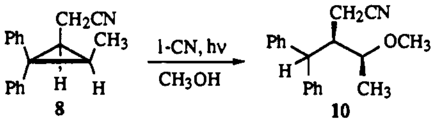
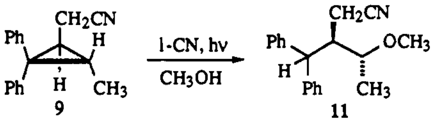
of the large rate constants for these reactions, an "early" transition state with a long nucleophile–carbon separation is expected, which should lead to diminished steric effects. However, this explanation does not rationalize why nucleophiles prefer to add at the more hindered carbon atom. Since the preferential substitution at C2 rather than C3 must be due to energy differences between the two S_N2 transition states, we hypothesize that alkyl substituents stabilize positive charge at the carbon atom undergoing substitution, thereby reversing the normal regiochemistry of substitution. The electronic effects apparently overwhelm the smaller steric effects in the three-electron S_N2 transition states. Our Hammond postulate argument for early transition state structures further suggests that the transition-state charge distributions may be similar to those of the ground-state cation radicals. EPR and CIDNP investigations on unsymmetrically substituted cyclopropane cation radicals show that the unpaired spin density (and presumably the charge distribution) is principally located in the more highly substituted cyclopropane bonds.[9] These data further support our proposed explanation.

Cyclopropanes **8** and **9** were prepared to test our electronic hypothesis.[10] Here, the substituents at C2 and C3 are comparable sterically but different electronically. Photooxidation of racemic **8** and **9** in methanol leads exclusively to formation of racemic, threo **10** and erythro **11**, respectively. Both of these products are the result of nucleophilic substitution with inversion of configuration at the carbon atom which bears the more electron-donating alkyl substituent.





In summary, three-electron S_N2 substitutions on diarylcyclopropane cation radicals by methanol are dominated by electronic rather than steric factors.[11] This leads to the surprising result that substitutions occur at the more hindered center, even when it is tertiary or neopentyl.

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(10) Prepared by the rhodium acetate catalyzed[9a,b] reaction of 1,1-diphenylpropene[9c] and ethyl diazoacetate. The cis and trans cyclopropyl esters so obtained were separated by medium-pressure column chromatography (SiO_2, 97:3 hexane/ethyl acetate). The esters were then reduced with lithium aluminum hydride in tetrahydrofuran. The resulting alcohols were converted into tosylates (tosyl chloride, pyridine, 0 °C), which were then converted into **8** and **9** by reaction with tetraethylammonium cyanide in dimethyl sulfoxide (25 °C, 8 h). (a) Anciaux, A. J.; Hubert, A. J.; Noels, A. F.; Petiniot, N.; Teyssié, P. *J. Org. Chem.* **1980,** *45,* 695. (b) Doyle, M. P.; Dorow, R. L.; Buhro, W. E.; Griffin, J. H.; Tamblyn, W. H.; Trudell, M. L. *Organometallics* **1984,** *3,* 44. (c) Simes, B. E.; Rickborn, B.; Flournoy, J. M.; Berlman, I. B. *J. Org. Chem.* **1988,** *53,* 4613.

(11) In general, the balance between electronic and steric factors in three-electron S_N2 reactions is not yet clear. Variations in both the structure of the cation radical and the nucleophile may well provide cases where, for example, a later transition state structure (with a shorter carbon–nucleophile separation) results in steric effects large enough to overwhelm the electronic effects.

Selective Catalytic Debromination by C_{60} Mono-, Di-, and Trianion[1]

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The fullerenes have stimulated intense interest and activity with regard to their structures, properties, and reactivities.[2-6] Several reports have demonstrated hydrogenation,[7] halogenation,[8] alkylation,[9] epoxidation,[10] and recently, the dimerization of radical adducts.[11] Several voltammetric studies of C_{60} also have appeared.[7,12-21] Generally, it has been found that C_{60} will undergo stepwise reduction in solution by up to six electrons,[18] depending on the experimental conditions. The long lifetime of the anions in solution and the nearly equal spacing of the voltammetric reduction waves suggest that it should be possible to use C_{60} as a highly selective intermolecular electron transfer catalyst for a wide range of reducible species. In this communication we report rate constants for electron-transfer reactions of C_{60} anion, dianion, and trianion with a number of bromides and vicinal dibromides. The implication of these results is that a single redox catalyst can be used to carry out a selective, stepwise, multistep reduction of complex organic compounds. To our knowledge, these are the first reported examples of homogeneous redox catalysis by C_{60} anions.

Voltammetric data for C_{60}, benzoquinone (BQ), 9,10-dicyanoanthracene (DCA), and 1,4-dicyanonaphthalene (DCN) in toluene/acetonitrile (5.4:1 v/v) containing 0.1 M tetrabutylammonium perchlorate (TBAP) as the supporting electrolyte are given in Table I. Also included are the irreversible peak potentials for the bromides used in this study. The application of homo-

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