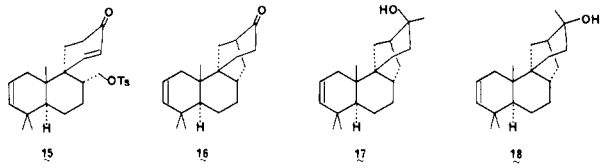

15 16 17 18

in liquid ammonia at −78 °C. The overall yield of **16** [mp 103–105 °C; IR_{max} ($CHCl_3$) 1710 cm^{-1}; ^1H NMR δ 1.01 (s, 3 H, CH_3), 0.97 (s, 3 H, CH_3), 0.93 (s, 3 H, CH_3)] from aldehyde **12** was 50% after chromatography on silica gel.

The next task, stereospecific introduction of C-18, was problematical since examination of molecular models did not indicate a preferred direction of carbonyl addition with respect to the bicyclo[3.2.1]octanone system. Methyllithium in ether at 0 °C reacted with **16** to give a mixture (~1:1) of tertiary alcohols **17** [mp 119–122 °C] and **18** [mp 147–149 °C, sublimes], R_f 0.37 and 0.31, respectively, after one elution by using 30% THF in hexane.[13] Trimethyl aluminum,[14] lithium tetramethylaluminate, and lithium trimethylmanganate[15] were also not selective. Methylmagnesium bromide in ether at 23 °C furnished alcohols **17** and **18** in the ratio of 2.4:1 (85% yield). Nonetheless, adequate stereoselectivity was obtained with dimethylsulfoxonium methylide[16] in dimethyl sulfoxide as reagent at 23 °C. Reduction of the isomeric spiro epoxides so obtained with lithium triethylborohydride[17] in THF at 23 °C afforded cleanly **17** and **18** in a ratio of 5:1. The improved selectivity is probably a reflection of a favored product-determining elimination of dimethyl sulfoxide from one of the reversibly formed ylide–carbonyl adducts of **16**.

Treatment of **17** at 23 °C in acetone with a solution of *N*-bromoacetamide (7.6 equiv) in water[18] followed by extractive workup with methylene chloride gave a single bromohydrin which was directly oxidized to the corresponding α-bromo ketone with PCC[6] in methylene chloride and debrominated with zinc dust in ether–aqueous ammonium chloride at 23 °C to afford synthetic (±)-stemodinone (**2**) [80%; mp 199–201 °C; IR_{max} (neat) 3392, 1689 cm^{-1}; ^1H NMR δ 1.13 (s, 3 H, CH_3), 1.09 (s, 3 H, CH_3), 0.97 (s, 3 H, CH_3), 0.93 (s, 3 H, CH_3)] which was spectroscopically and chromatographically identical with natural stemodinone.[19] (±)-Stemodinone was reduced to (±)-stemodin (**1**) [mp 218–220 °C; IR_{max} (neat) 3330 cm^{-1}; ^1H NMR δ 1.12 (s, 3 H, CH_3), 0.99 (s, 3 H, CH_3), 0.95 (s, 3 H, CH_3), 0.92 (s, 3 H, CH_3)] with sodium in THF–ethanol at 0 °C in 43% overall yield from **17**.[20,21] Natural and synthetic **1** were identical by IR, ^1H NMR, and mass spectra and thin-layer chromatography in three solvent systems.[22]

(13) The stereochemistry of the tertiary alcohols **17** and **18** was assigned by comparing the observed ^1H NMR chemical shifts of the carbinol methyl groups with the reported[1] data for stemodin (**1**): δ 1.08 for stemodin, vs. 1.24 for **18** and 1.12 for **17**.

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(19) We are indebted to Dr. Percy S. Manchand for generous samples of natural stemodin and stemodinone.

(20) Sodium borohydride reduced **2** to the 2β-alcohol.

(21) In connection with our synthesis see, Chatterjee, S. *J. Chem. Soc., Chem. Commun.* **1979**, 622. It must be noted that our observed ^1H NMR chemical shifts of the methyl groups of 3-desoxystemodin (in $CDCl_3$) [δ 0.88 (s, 6 H, $2CH_3$), 0.96 (s, 3 H, CH_3), 1.11 (s, 3 H, CH_3)] differ from the reported data of Chatterjee [δ 0.90 (s, 3 H, CH_3), 0.93 (s, 3 H, CH_3), 0.97 (s, 3 H, CH_3), 1.13 (s, 3H, CH_3)]. See also Cornforth, J. *Tetrahedron Lett.* **1980**, *21*, 709.

(22) This research was assisted financially by a grant from the National Science Foundation.

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Solvolysis of Adamantanone Cyanohydrin Sulfonates. An Evaluation of H/α-CN vs. H/β-CN Rate Ratios

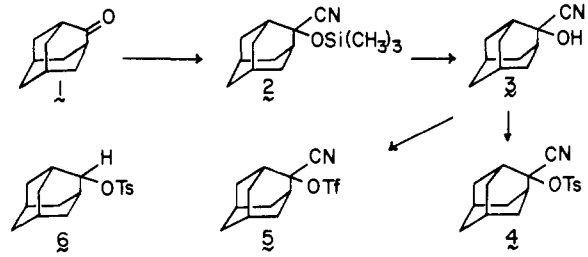
Sir:

We have recently provided both experimental[1] and theoretical[2] evidence that a cyano function attached directly to a carbocation can provide resonance stabilization which almost balances its inductive destabilization. In addition, our theoretical studies[2] suggested that an α-cyano substituent should be less destabilizing than a β-cyano substituent to an electron-deficient cationic center. These theoretical predictions could be experimentally evaluated in terms of H/α-CN vs. H/β-CN rate ratios. We now present experimental evidence which supports our theoretical calculations.

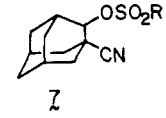
Because of its structural rigidity and its steric blockage of backside displacement of attached leaving groups by solvent, the tricyclo[3.3.1.$1^{3,7}$]decyl (adamantyl) skeleton has been widely employed as a standard substrate for the study of the properties of carbonium ions.[3,4] In view of these well-established characteristics, we felt that the adamantyl skeleton would serve as an ideal substrate for evaluating the relative effects of H, α-CN, and β-CN on the ease of ionization of sulfonate esters. Treatment of adamantanone (**1**) with trimethylsilyl cyanide and a catalytic amount of zinc iodide gave **2**, which on hydrolysis with 3 N hydrochloric acid according to our general procedure[5] gave adamantanone cyanohydrin[6] (**3**) in 95% overall yield. Addition of *p*-toluenesulfonic anhydride to **3** gave a 92% yield of **4**,[7] mp 88–90 °C. In a similar manner, **3** reacted with trifluoromethanesulfonic anhydride to give 92% of **5**, mp 48–49 °C.

For rate comparisons, **6** was prepared according to the literature procedure.[4]

Table I lists the rates observed for the solvolysis of **4–6** in 100%



2,2,2-trifluoroethanol buffered with 2,6-lutidine[8] and of **5** in 90% aqueous acetone. As can be noted from a comparison of **4** and **6**, the H/α-CN rate ratio is 2.1×10^3. This rate ratio is extremely close to the value of 1.9×10^3 observed for cyclooctyl tosylate vs. the tosylate of cyclooctanone cyanohydrin.[1] Since Farcasiu[4g,h] has studied the solvolysis of **7** (R = CH_2CF_3) and found a H/



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(7) Satisfactory elemental analyses and/or exact mass molecular weights were obtained on all new compounds.

(8) For the basis for the use of anhydrous 2,2,2-trifluoroethanol, see ref 1.

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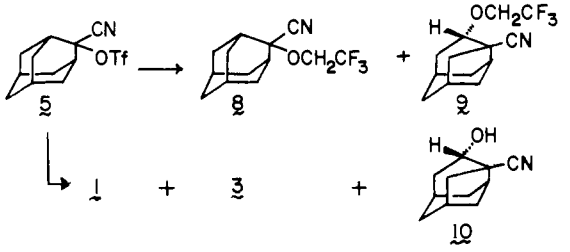
Table I. Rates of Solvolysis of Sulfonate Esters Derived from 2-Adamantanol and 2-Cyano-2-adamantanol

compd	temp, °C (±0.02 °C)	solvent[a]	rate,[b] s^{-1}	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu
6	90.00	A	$(2.00 \pm 0.02) \times 10^{-3}$		
	75.00		$(6.38 \pm 0.02) \times 10^{-4}$		
	60.00		$(1.35 \pm 0.01) \times 10^{-4}$	20.0 ± 0.1	−13.5 ± 1.9
	25.0[c]		3.04×10^{-6}		
4	155.00	A	$(3.71 \pm 0.05) \times 10^{-4}$		
	140.00		$(1.47 \pm 0.01) \times 10^{-4}$		
	125.00		$(4.27 \pm 0.12) \times 10^{-5}$	23.6 ± 0.8	−19.6 ± 2.0
	25.0[c]		1.44×10^{-9}		
5	45.00	A	$(9.20 \pm 0.15) \times 10^{-3}$		
	35.00		$(2.93 \pm 0.07) \times 10^{-3}$		
	24.80		$(8.73 \pm 0.15) \times 10^{-4}$	21.3 ± 0.2	−0.9 ± 0.8
	25.0[c]		8.73×10^{-4}		
5	40.00	B	$(1.68 \pm 0.10) \times 10^{-3}$		
	30.00		$(6.18 \pm 0.05) \times 10^{-4}$		
	20.00		$(2.27 \pm 0.03) \times 10^{-4}$	20.3 ± 0.4	−6.0 ± 1.4
	25.0[c]		4.54×10^{-4}		

[a] Solvent A was 100% 2,2,2-trifluoroethanol buffered with 2,6-lutidine; solvent B was 10:90 (v/v) water–acetone buffered with 2,6-lutidine. [b] All rates were measured conductometrically. [c] Extrapolated from other temperatures.

β-CN rate ratio of 1.3×10^5, a H/α-CN vs. H/β-CN comparison can be made. *This comparison shows that a β-cyano substituent is approximately 10^2 times more rate retarding than an α-cyano substituent in spite of the closer proximity of the α-cyano group.* These data leave little doubt concerning the strong resonance stabilization of a carbocationic center by an α-cyano moiety.

Product studies were achieved by using the triflate **5**, in order to minimize the temperature required. Solvolysis of **5** in 100% 2,2,2-trifluoroethanol gave 88% of **8** and 8% of **9**.[9] The structure of **8** was established on the basis of its elemental analysis and the very close resemblance of both its proton and carbon-13 NMR spectra to those of **3** and **4**. The structure of **9** presented greater difficulties. NMR spectral studies established that skeletal rearrangement had occurred and mass spectral measurements and elemental analysis indicated that **8** and **9** were isomeric.



In order to further establish the structure of **9**, we studied the solvolysis of **5** in 10:90 (v/v) water–acetone. This solvolysis gave 31% of adamantanone (**1**), 31% of adamantanone cyanohydrin (**3**), and 30% of **10**. The ^1H NMR spectrum of **10** showed a one-proton triplet at δ 4.30 (J = 4.0 Hz). The 4-endo protons of 4-*exo*-protoadamantanol[4d] and 8-cyano-4-*exo*-protoadamantanol[4g,h] appeared at δ 4.38 and 4.27, respectively.[10] NMR spectroscopic comparisons established that **9** was the 2,2,2-trifluoroethyl ether of **10**.

In order to unequivocally establish the structure of the rearrangement product, we performed a single-crystal X-ray analysis of **10** (mp 206.0–206.5 °C). The white crystals of $C_{11}H_{15}NO$ belonged to the orthorombic space group $Pna2_1$. The measured cell constants, a = 10.388 (2) Å, b = 7.128 (2) Å, and c = 11.983 (2) Å, gave a calculated density of 1.279 g/cm^3 for four molecules in the unit cell at ambient temperature. Data were collected on a fully automated Enraf-Nonius CAD4 diffractometer, using a variable scan rate ω–2θ scan technique and graphite-monochromatized Mo Kα radiation (λ 0.71069 Å). After Lorentz–polarization corrections, 674 of 862 unique reflections (78%) with 2θ = 0–50° were observed for $[F_o \geq 2\sigma(F_o)]$. A combination of direct methods and Fourier synthesis was used to locate all nonhydrogen atoms.[11] Thermal anisotropic refinement was applied to all nonhydrogen atoms. The positions of all hydrogen atoms were calculated. The R factor for the structure was 0.038. Figure 1 is an ORTEP drawing of **10** with the hydrogens omitted for clarity. Tables of bond lengths, bond angles, and atom coordinates are available as supplementary material. These data firmly establish the structure of **10** to be that with the protoadamantyl skeleton.

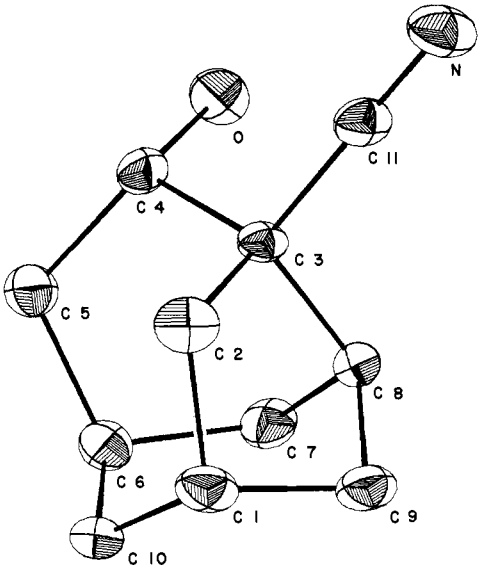
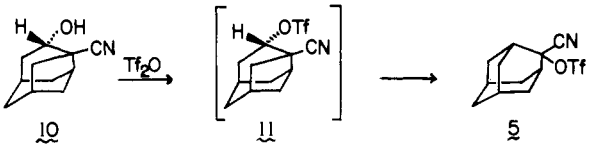


Figure 1. ORTEP drawing of **10**.

In an attempt to extend our concept of the ionic intermediate which was a precursor of **10**, we treated **10** with trifluoromethanesulfonic anhydride in anticipation of isolating **11**. We



(9) Control experiments demonstrated that **8** and **9** were not interconverted under the reaction conditions used in the solvolysis.

(10) For a detailed review of tricyclo[4.3.1.$0^{3,8}$]decane (protoadamantane) behavior see ref 3, pp 35–61.

(11) All calculations were carried out on a PDP 11/34 computer, using the Enraf-Nonius SDP programs. This crystallographic computing package is described by B. A. Frentz in "Computing in Crystallography", H. Schenk, R. Olthof-Hazekamp, H. van Konigweld, and G. S. Bassie, Eds., Delft University Press, Delft, Holland, 1978, pp 64–71.

were not able to isolate or detect **11**. Instead, we found that this reaction gave a 76% yield of **5**. It is presumed that **11** rearranges to **5** via a tight ion-pair mechanism under the conditions of its generation. This again would imply that the α-cyano-substituted cation is more stable than the β-cyano-substituted cation.[12,13]

In summary, we have demonstrated that the H/α-CN rate ratio is approximately 10^3 in contrast to the value of 10^5 observed for a H/β-CN rate ratio in the same system. These experimental results are in agreement with our earlier theoretical calculations. We are continuing our studies in this area.

Acknowledgment. We are indebted to the National Science Foundation for Grant CHE78-10231, which supported this investigation, and for Grant CHE77-28505, which aided in the purchase of an Enraf-Nonius X-ray diffractometer. We thank Mr. M. McGuiggen and Professor L. Pignolet for assistance in the X-ray study.

Supplementary Material Available: Tables of bond distances, bond angles, thermal parameters, and atom coordinates (5 pages). Ordering information is given on any current masthead page.

(12) An added factor which must be taken into consideration in the discussion is the relative thermodynamic stabilities of the adamantyl and protoadamantyl skeletons.

(13) The extremely mild conditions under which **10** gave **5** indicate that the equilibration of **5** and **11** (via a tight ion pair) occurs with great ease. The failure to isolate any **11** may be due to the selective crystallization of **5** with a resulting total conversion of **11** to **5**. Under equilibrating conditions, the concentration of **11** must be small since its presence is not obvious in solution spectra of **5**.

(14) Proctor and Gamble Fellow, 1977–1978; University of Minnesota Dissertation Fellow, 1978–1979.

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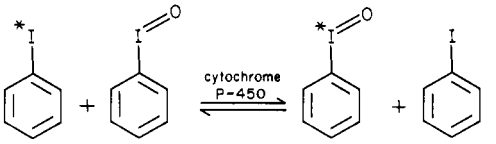
Enzymatic Monooxygenation of Halogen Atoms: Cytochrome P-450 Catalyzed Oxidation of Iodobenzene by Iodosobenzene

Sir:

Cytochromes P-450 are a class of hemoproteins that catalyze the monooxygenation of a variety of organic compounds.[1] The cytochrome P-450 containing mixed-function oxidase systems are thought to activate molecular oxygen via two sequential one-electron reductions, resulting in a highly reactive carbenelike FeO species.[2] A species presumed to be this FeO complex has been obtained with rat liver microsomes without a requirement for O_2 and NADPH, using iodosobenzene as an oxygen atom source.[3] Hydroxylated products have been observed from the reaction of iron porphyrin complexes with iodosobenzene or iodosoxylene.[4] It has been postulated that these hydroxylations also proceed via an FeO species.

Recently we have explored the possibility that cytochrome P-450 mixed-function oxidases metabolize some halogenated compounds via an initial halogen oxidation to form an R—X=O intermediate. Evidence has been presented that at least part of the metabolism of 1,2-dichloroethane by P-450 may proceed through a chlorine oxide (chloroso) intermediate.[5]

A system in which formation of a halogen oxide might easily be demonstrated is the P-450-catalyzed oxygenation of iodobenzene. As mentioned earlier, iodosobenzene has been used as an oxygen atom source for P-450 and, in principle, this reaction should be reversible. To investigate this possibility, we have studied the equilibration between unlabeled iodosobenzene and [^{125}I]-iodobenzene.[6]



One milliliter of a pH 7.4 solution 0.22 μM in P-450 (purified to apparent homogeneity from phenobarbital-induced rat liver),[7] 5 mM in iodosobenzene, 1 mM in [^{125}I]iodobenzene (0.9 μCi/μmol), and 0.1 mM in EDTA was incubated at 37 °C for 2 min. The incubation mixture was then cooled to 0 °C and 50 μL of 1 M $ZnSO_4$ was added. After the mixture stood at 0 °C for 10 min, 100 μL of acetic anhydride was added to convert the iodosobenzene to iodobenzene diacetate [$PhI(OAc)_2$].[8] After this mixture stood at 23 °C for an additional 30 min, a 50-μL aliquot of the mixture was analyzed by high-performance LC by using two 30-cm μ-Bondapak phenyl columns connected in series with 2.5:1 methanol–water (1.75 mL/min) as the mobile phase. Fractions were collected and assayed in a liquid scintillation spectrometer. Under these conditions 14.0 nmol of [^{125}I]$PhI(OAc)_2$ was formed.

The amount of labeled $PhI(OAc)_2$ detected was a nonlinear function of the cytochrome P-450 concentration. Thus 0.11 μM P-450 yielded 10 nmol of [^{125}I]$PhI(OAc)_2$, and 1.1 μM P-450 produced 62 nmol of the labeled diacetate.[9] At higher P-450 concentrations, however, the high-performance LC peak corresponding to $PhI(OAc)_2$ was diminished and the radioactivity became more diffusely spread throughout the chromatogram. An incubation with a P-450 concentration of 2.6 μM gave no more than 30 nmol of labeled $PhI(OAc)_2$. Since iodosobenzene is a strong oxidizing agent, it is to be expected that some will be lost as a result of protein or heme oxidation. As the concentration of P-450 was increased (and therefore the concentration of possible reducing agents for iodosobenzene increased), the amount of iodosobenzene surviving the incubation decreased. In the absence of cytochrome P-450 no radioactivity was detected in the $PhI(OAc)_2$ peak.

Iodobenzene diacetate has also been used as an oxygen source for P-450.[3,10] Presumably the diacetate is hydrolyzed in situ to iodosobenzene. When unlabeled $PhI(OAc)_2$ was substituted for iodosobenzene in the incubation mixture containing 0.22 μM P-450, 178 nmol of [^{125}I]$PhI(OAc)_2$ was detected. However, if acetic anhydride was not added in the workup of the incubation mixture, there was no radioactivity in the $PhI(OAc)_2$ peak. Gustafsson et al.[10] report the (diacetoxyiodo)benzenes to be more efficient oxygen donors than the corresponding iodosobenzene.

Denaturing the P-450 by heating in 1% sodium dodecyl sulfate and removing the detergent blocked the oxygen transfer. Also, when the heme was removed from the protein by treatment with

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(6) Prepared by adding K[^{125}I] to diazotized aniline. The [^{125}I]iodobenzene was isolated by short-column chromatography on silica gel with pentane as solvent. The material was homogeneous by high-performance LC analysis.

(7) Guengerich, F. P. *J. Biol. Chem.* **1978**, *253*, 7931.

(8) This was done since we were unable to separate iodobenzene cleanly from iodosobenzene with any high-performance LC system. The conversion to $PhI(OAc)_2$ resulted in a 7.5-min separation of PhI and $PhI(OAc)_2$ peaks.

(9) Iodophenols, the expected hydroxylation products, could not be detected with certainty in the high-performance LC as they eluted too near the void volume. Although there was no clearly discernible peak, from the amount of radioactivity in the region of the *p*-iodophenol retention time, there could be as much as 9 nmol of iodophenol formed in the 1.1 μM P-450 incubation.

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