water was added 0.168 g (1 mmol) of **2c**. The reaction mixture was stirred and mixtures of 2 g of sucrose and 3 g of yeast were added every 48 h. After 1 week the consumption of **3c**, which formed within 12 h, had slowed appreciably and the reaction was stopped by centrifugation and extraction of the supernatant with ether (4 × 25 mL). The extract was dried over anhydrous $MgSO_4$ and concentrated in vacuo to afford 0.19 g of an oil, which upon evaporation under 0.25 mmHg with trapping on a cold finger at −78 °C afforded **1c** and **5c**: 15 mg, 9%, **1c**:**5c**, 2:1, DB-1, program 1. Optical purity: (+)-**1c**, ee 92%; (−)-**5c**, ee 45% (complexation chromatography, Ni-4-Pin). ^1H NMR ($CDCl_3$) δ: 0.97 (t, J = 7.5, 3 H), 1.44 (s, 3 H), 1.3–1.9 (m, 10 H), 4.04 (m, 1 H), 4.18 (m, 1 H). M_r calcd for $C_{10}H_{18}O_2$ 170.1307, found (high resolution MS) 170.1307. The residue upon Kugelrohr distillation afforded 0.08 g (43%) of **3c** as a hygroscopic liquid, bp 120 °C (0.2 mmHg): IR (film) 3450, 1712 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (t, J = 7.5 Hz, 3 H), 1.20–2.04 (m, 6 H), 2.14 (s, 3 H), 2.50 (m, 4 H), 3.09 (br s, 1 H), 4.15 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.62, 16.99, 19.08, 29.76, 32.74, 39.64, 42.87, 76.15, 187.23, 190.87; low resolution CIMS (isobutane), m/e 187 ($M + H^+$). Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.76; H, 10.05.

Bakers' Yeast Reduction of 3c. Ketone **2c**, 0.33 g (2 mmol), was stirred with 2 mL of 0.05 M KH_2PO_4 for 20 h and the resulting clear solution was added to an actively fermenting mixture of 3 g of bakers' yeast and 0.5 g of sucrose in 10 mL of water. Additional 0.5-g amounts of sucrose were added every 24 h and 1.5-g quantities of yeast every 48 h. After stirring for 8 days and workup as above were obtained **1c** and **5c**: 0.026 g, 7.5%, **1c**:**5c**, 30:1, DB-1, program 1. Optical purity: (+)-**1c**, ee 98%; (−)-**5c**, ee 34% (complexation chromatography, Ni-4-Pin).[11]

Acknowledgment. This work was funded by a Natural Sciences and Engineering Research Council Strategic Grant (Biotechnology) and an Operating Grant to A.C.O. We thank Professor Hal Wieser and Dr. Elizabeth Dixon of the Department of Chemistry at the University of Calgary for helpful discussions and preliminary communication of their work in this area.

Registry No. (+)-**1a**, 22625-19-0; (−)-**1a**, 80952-67-6; (+)-**1b**, 117957-12-7; (+)-**1c**, 117897-06-0; (*S*)-**2a**, 117957-11-6; (±)-**2a**, 117957-10-5; (±)-**2b**, 84498-69-1; (±)-**2b** *N*-cyclohexyl imine, 117897-02-6; (±)-**2c**, 117897-03-7; (*S*)-**3a**, 117897-04-8; (−)-**5b**, 117957-13-8; (−)-**5c**, 117957-14-9; (*S*)-**7**, 117897-05-9; bromoethane, 74-96-4.

Some Observations on the Mechanism of the Mitsunobu Reaction

David Crich,* Hubert Dyker, and Robert J. Harris

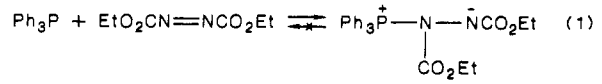
Department of Chemistry, University College London, 20, Gordon Street, London, WC1H OAJ, U.K.

Received June 27, 1988

During a search for a stereoselective preparation of secondary alkyl hydroperoxides, we examined some aspects of the mechanism of the Mitsunobu reaction and studied the use of *m*-chloroperoxybenzoic acid (MCPBA) as a nucleophile.

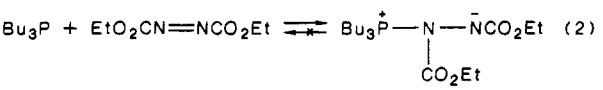
The triphenylphosphine (TPP)/diethyl azodicarboxylate (DEAD) mediated esterification of an alcohol with an acid, with clean inversion of configuration for asymmetric alcohols, known[1] as the Mitsunobu reaction, has been subjected[2] to considerable mechanistic scrutiny in recent years. The majority of this work relates to the later stages of the mechanism and concerns the intermediacy of alkoxyphosphonium salts and/or dialkoxyphosphoranes. The work described below focuses on the initial stages of the mechanism and provides supportive evidence for the irreversibility[2b] of the addition of TPP to DEAD.

Literature methods for the stereoselective preparation of secondary alkyl hydroperoxides involving[3] the displacement of mesylates by alkaline hydrogen peroxide give at best meagre yields, although application[4] to primary mesylates is more efficient. The use of potassium superoxide/18-crown-6 in dimethyl sulfoxide/dimethylformamide yields[5] alcohols and not hydroperoxides. More efficient methods for the preparation of secondary hydroperoxides involve either free radical[6] or carbocation[7] intermediates and are nonstereoselective. We conceived that the use of MCPBA as nucleophile in the Mitsunobu reaction with a secondary alcohol would provide secondary peroxyesters, with clean inversion of configuration, and that alkaline hydrolysis would then yield[8] diastereomerically pure secondary alkyl hydroperoxides. Obvious problems such as oxidation of TPP by the peracid would be circumvented by prior formation of the betaine and dialkoxyphosphoranes before addition of MCPBA. Such an approach relies on clean, *irreversible*, betaine formation. Although Guthrie and Jenkins noted[2b] that the ^{31}P NMR chemical shift of the betaine showed little solvent dependence (δ +43.9 in benzene; +44.7 in chloroform; +45.4 in dimethylformamide) and took this to imply little or no equilibrim with TPP and DEAD, we sought more conclusive evidence for the irreversibility of this reaction (eq 1).



$$Ph_3P + EtO_2CN{=}NCO_2Et \rightleftharpoons Ph_3\overset{+}{P}-\underset{\displaystyle CO_2Et}{\underset{|}{N}}-\overset{-}{N}CO_2Et \quad (1)$$

Equimolar amounts of TPP and DEAD were allowed to react in THF to give the betaine. Clean formation of the betaine (δ +43) was observed, and all of the TPP (δ −5.3) was consumed. An equimolar quantity of tributylphosphine (TBP) was then added and the ^{31}P NMR spectrum recorded after 20 min. Some formation of triphenylphosphine oxide (δ +23) was observed, presumably due to hydrolysis by extraneous water, but, significantly, no TPP was liberated, indicating that the reaction of eq 1 is not reversible, at least on the time scale of a typical Mitsunobu reaction. This observation was given further credence when addition of TPP to a preformed solution of the betaine from TBP and DEAD (eq 2) (δ +46) did not lead to the liberation of TBP (δ −32) or formation of the TPP/DEAD betaine.



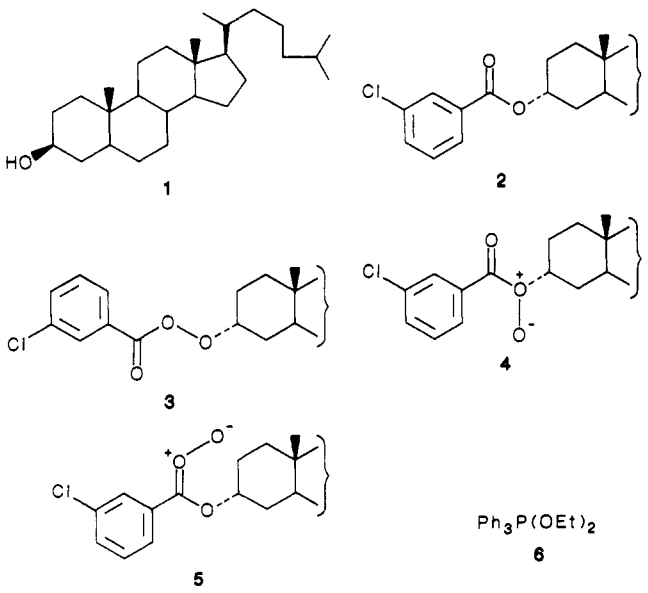
$$Bu_3P + EtO_2CN{=}NCO_2Et \rightleftharpoons Bu_3\overset{+}{P}-\underset{\displaystyle CO_2Et}{\underset{|}{N}}-\overset{-}{N}CO_2Et \quad (2)$$

Secure in the knowledge that prior betaine formation would exclude the reaction of TPP with MCPBA, we attempted the formation of peresters by the Mitsunobu se-

(1) Mitsunobu, O. *Synthesis* **1981**, 1 and references therein.
(2) (a) Grochowski, E.; Hitton, B. D.; Kupper, R. J.; Michejda, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 6876. (b) Guthrie, R. D.; Jenkins, I. D. *Aust. J. Chem.* **1982**, *35*, 767. (c) von Itzstein, M.; Jenkins, I. D. *Aust. J. Chem.* **1983**, *36*, 557. (d) Varasi, M.; Walker, K. A. M.; Maddox, M. L. *J. Org. Chem.* **1987**, *52*, 4235.
(3) Williams, H. R.; Mosher, H. S. *J. Am. Chem. Soc.* **1954**, *76*, 2987.
(4) (a) Williams, H. R.; Mosher, H. S. *J. Am. Chem. Soc.* **1954**, *76*, 2984. (b) Wawzonek, S.; Klimstra, P. D.; Kallio, R. E. *J. Org. Chem.* **1960**, *25*, 621.
(5) Corey, E. J.; Nicolaou, K. C.; Shibasaki, M.; Machida, Y.; Shiner, C. S. *Tetrahedron Lett.* **1975**, 3186.
(6) Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron* **1985**, *41*, 3901.
(7) Cagliotti, L.; Gasparrini, F.; Misiti, D.; Palmieri, G. *Tetrahedron* **1978**, *34*, 135.
(8) Milas, M. A.; Surgenor, D. M. *J. Am. Chem. Soc.* **1946**, *68*, 642.

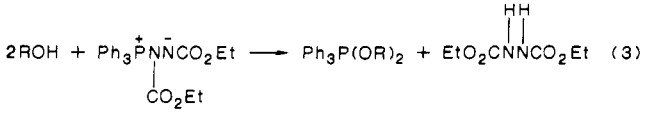
0022-3263/89/1954-0257$01.50/0

Chart I



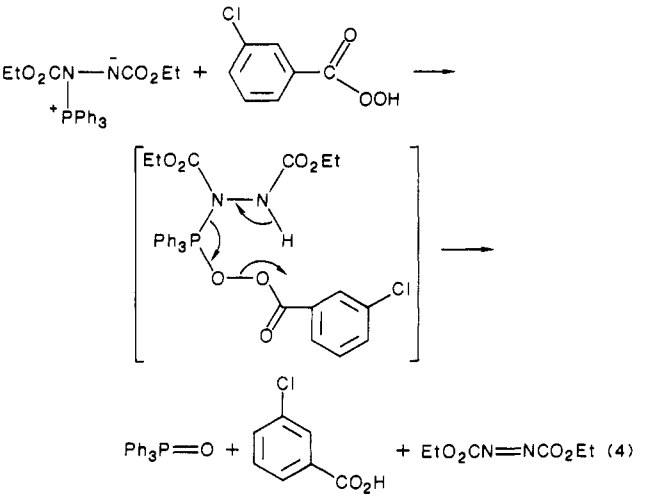
quence. A 1:1.1 mixture of 3β-cholestanol (1) and TPP in THF was treated with 1.1 equiv (wrt 1) of DEAD, and after 30 min at room temperature purified[9] MCPBA was added. Chromatographic workup gave, reproducibly, 3α-cholestanyl *m*-chlorobenzoate (2) in 44% yield (Chart I). The identity of 2 was confirmed by preparation of an authentic sample by the Mitsunobu reaction of 1 with *m*-chlorobenzoic acid. Several, very minor, unidentified steroidal products were also present in the final reaction mixture together with significant amounts of unreacted starting materials 1 and MCPBA.

At first several explanations are possible for the above result. It could be that the reaction of MCPBA with either the intermediate dialkoxyphosphorane or the alkoxyphosphonium salt leads not to the desired perester 3 but to the ylides 4 and/or 5 which then undergo deoxygenation to 2. We consider this possibility unlikely; to our knowledge, MCPBA has yet to be reported as a nucleophile in S_N2-type reactions, but its use as a nucleophile at sp^2 centers is well documented[10] and would appear to indicate that the nucleophilic center is the peroxygen. A second possibility is that perester 3 forms initially and then undergoes deoxygenation, in situ, to 2. This we exclude on the grounds that no free TPP is available to bring about the deoxygenation and also that the reported conditions[11] for such deoxygenations are considerably more vigourous than those applied here. A much more plausible explanation involves formation of a dialkoxyphosphorane from 2 mol of alcohol and one of betaine (eq 3). According to the stoichiometry of the reaction, and, as verified by Jenkins,[2c] 1 mol of betaine would remain unreacted.



This residual mole of betaine is then available to react with MCPBA according to eq 4, giving ultimately DEAD, triphenylphosphine oxide, and *m*-chlorobenzoic acid. *m*-Chlorobenzoic acid generated in this manner can then react with the phosphorane of eq 3, with or without the intermediacy of an alkoxyphosphonium salt, to give reaction product 2.

The maximum yield of 2 available by this mechanism would be 50%, in reasonable agreement with the observed yield of 44%. The hypothesis outlined in eq 4 was readily



verified in a qualitative manner: thus addition of MCPBA to a THF solution of the betaine gave immediately triphenylphosphine oxide, *m*-chlorobenzoic acid, and DEAD all of which were identified in the reaction mixture by TLC and ^1H NMR spectroscopy. Further supportive evidence is provided[12] by the observations of Jenkins on the reaction of the same betaine with hydrogen peroxide.

Finally attempts at the reaction of MCPBA with phosphorane 6 (δ +54), prepared from TPP and excess diethyl peroxide according[13] to Denney, gave triphenylphosphine oxide virtually quantitatively and minor amounts of a compound identified as ethyl *m*-chlorobenzoate but apparently none of the corresponding perester.

In conclusion, although unsuccessful in our objective of preparing secondary alkyl hydroperoxides, we have provided evidence for the irreversibility of betaine formation between TPP and DEAD. Moreover, our results support the independent work of Grochowski[2a] and Jenkins[2c] on the formation of dialkoxyphosphoranes, prior to the addition of an acidic component, in the Mitsunobu reaction.

Experimental Section

Melting points were taken on a Reichert hot stage apparatus and are uncorrected. Optical rotations were measured for chloroform solutions with an Optical Activity AA10 polarimeter. IR spectra were recorded with a Perkin-Elmer 983 spectrophotometer; 70 eV mass spectra were recorded with a VG 7070H mass spectrometer. ^1H NMR spectra were recorded at 60 MHz with a JEOL PMX 60 SI spectrometer and at 200 MHz with a Varian XL 200 instrument. ^1H chemical shifts for deuteriochloroform solutions are in ppm downfield from tetramethylsilane as internal standard. Proton-decoupled ^{31}P NMR spectra were recorded at 32 MHz with a Varian CFT 20 spectrometer; positive chemical shifts are in ppm downfield from 85% phosphoric acid as external standard.

Reaction of *m*-Chloroperoxybenzoic Acid with 3β-Cholestanol, Triphenylphosphine, and Diethyl Azodi-

(9) Schwartz, N. N.; Blumbergs, J. H. *J. Org. Chem.* **1964**, *29*, 1976.
(10) See inter alia: (a) Fieser and Fieser *Reagents for Organic Synthesis* **1967**, *1*, 137. (b) Meinwald, J.; Tufariello, J. F.; Hurst, J. J. *J. Org. Chem.* **1964**, *29*, 2914. (c) Brown, H. C.; Kabalka, G. W.; Rathke, M. W. *J. Am. Chem. Soc.* **1967**, *89*, 4530. (d) Whitesell, J. K.; Matthews, R. S.; Helbling, A. M. *J. Org. Chem.* **1978**, *43*, 784. (e) van der Linde, L. M.; van der Weerdte, A. J. A. *Tetrahedron Lett.* **1984**, *25*, 1201. (f) Yamamoto, S.; Itani, H.; Tsuji, T.; Nagata, W. *J. Am. Chem. Soc.* **1983**, *105*, 2908.
(11) Denney, D. B.; Goodyear, W. F.; Goldstein, B. *J. Am. Chem. Soc.* **1961**, *83*, 1726.
(12) von Itzstein, M.; Jenkins, I. D. *J. Chem. Soc., Chem. Commun.* **1983**, 164.
(13) Denney, D. B.; Denney, D. Z.; Wilson, L. A. *Tetrahedron Lett.* **1968**, 85.

carboxylate: Optimized Conditions. Diethyl azodicarboxylate dried over 4-Å molecular sieves (191 mg, 1.1 mmol) was added to a solution of 3β-cholestanol (388 mg, 1.1 mmole), triphenylphosphine (288 mg, 1.1 mmol), and 2,6-lutidine (137 mg, 1.1 mmol) in dry distilled THF (10 mL) and stirred at room temperature. After 5 min purified[9] MCPBA (188 mg, 1.1 mmol) was added to the reaction mixture and stirring continued at room temperature for 5 h. After removal of the solvent, in vacuo, column chromatography (SiO_2; eluent pertroleum spirit (40–60)/diethyl ether 98:2) of the crude reaction mixture gave the ester **2** (230 mg, 44%) as a colorless crystalline solid identical with an authentic sample (described below). Further elution with mixtures of petroleum ether and ether gave recovered 3β-cholestanol and then triphenylphosphine oxide (250 mg; 83%).

3α-Cholestanyl *m*-Chlorobenzoate: Preparation of an Authentic Sample. Diethyl azodicarboxylate (191 mg, 1.1 mmol) was added at room temperature to a stirred solution of 3β-cholestanol (388 mg, 1 mmol) and triphenylphosphine (288 mg, 1.1 mmol) in dry toluene (10 mL) resulting in a bright orange/red coloration. *m*-Chlorobenzoic acid (172 mg, 1.1 mmol) was then added and the mixture was stirred at room temperature for 5 h before evaporation and chromatography on silica gel. Elution with 2% ether in petroleum ether gave the ester **2** (444 mg, 83%) as a white crystalline solid with mp 108–109 °C (acetone): $[\alpha]^{27}_D$ +11.3° (c = 1 in $CHCl_3$); NMR 0.65 (s, 3 H), 5.25 (m, 1 H, width at $^1/_2$ height = 7 Hz), 7.2 (m, 2 H), 7.9 (m, 2 H); IR (Nujol) 1725 cm^{-1}; MS, m/e 526 (M^+), 370, 355, 230, 215. Anal. Calcd for $C_{34}H_{51}ClO_2$ (527.232): C, 77.45; H, 9.75; Cl, 6.72. Found: C, 77.25; H, 9.59; Cl, 6.80.

Acknowledgment. H.D. thanks the Deutscher Akademischer Austauschdienst (DAAD) for an exchange fellowship.

Registry No. 1, 17608-41-2; 2, 117775-75-4; MCPBA, 937-14-4; $EtO_2CN{=}NCO_2Et$, 1972-28-7; Ph_3P, 603-35-0; Bu_3P, 998-40-3; $Ph_3P^+N(CO_2Et)N^-CO_2Et$, 58477-00-2; $Bu_3P^+N(CO_2Et)N^-CO_2Et$, 83053-10-5.

Intrazeolite Photochemistry. 5. Use of Zeolites in the Control of Photostationary Ratios in Sensitized Cis–Trans Isomerizations[1]

F. Gessner,[2a] A. Olea,[2b] J. H. Lobaugh,[2c] L. J. Johnston,* and J. C. Scaiano*

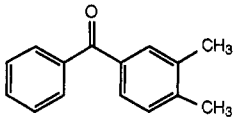
Division of Chemistry, National Research Council of Canada, Ottawa, Ontario, Canada K1A 0R6

Received August 26, 1988

During the last few years a number of publications from our and other laboratories have examined the possibility of controlling the course of photochemical and photophysical processes by using zeolite supports.[3-12] This control usually reflects limitations in the mobility of and/or access to specific zeolite sites by the included molecule. We have now explored the use of the hydrophobic zeolite Silicalite to control the photostationary composition in sensitized cis–trans isomerizations. As a model system we have chosen the well-documented isomerization of stilbene.[13]

Silicalite (>99% SiO_2) belongs to a relatively new class of dealuminized zeolites with a framework structure consisting of five SiO_2 units.[14] The channel system consists of near-circular zig-zag channels cross-linked by elliptical straight channels. The diameter of the circular channels is 5.4 ± 0.2 Å and the cross section of the elliptical ones 5.75 × 5.15 Å^2.

The triplet sensitizer selected for our experiments was 3,4-dimethylbenzophenone (DMBP). Earlier work had shown that benzophenone includes very poorly on Silicalite;[4] thus, we expect that the substitution pattern in DMBP will exclude it from the channel structure and that only absorption on the surface of Silicalite is likely.



DMBP

Examination of stilbene models suggests that the cis isomer should not fit in the channels of Silicalite, while the diameter of the trans isomer is such that it should be readily included. In solution the triplet-sensitized isomerization of stilbene yields sensitizer-dependent photostationary ratios, which normally contain a moderate excess of the cis isomer.

Experimental Section

Silicalite, S-115, from Union Carbide has a particle size of ~1 μm and was calcined (500 °C for 24 h) and then allowed to equilibrate in air before use. We have noted significant fluctuation in the properties of different batches of Silicalite. While these differences were not evident in terms of particle size or composition (as determined by electron micrographs and X-ray fluorescence), inclusion in some cases led to the development of green-blue colors. We suspect that the color may reflect radical-ion generation; it was observed not only with stilbene but also with a variety of biphenyls. The lot number used in this study (966184061053-S-1) did not present this problem, while lot 961883060011-S-1 was particularly prone to color development. While in this paper we make no attempt to characterize the origin of these problems we simply want to bring them to the attention of potential users of Silicalite.

The substrates and sensitizer were incorporated on the Silicalite samples by using the same technique described earlier[3-5] (with isooctane as a solvent/carrier), and the dried samples were irradiated with the light from a Hanovia 200-W mercury–xenon lamp, filtered through a solution of stilbene (initially trans) in benzene, to minimize direct photolysis of the Silicalite-supported stilbene. The samples were supported on a rotating disk during the irradiation to ensure mixing of the sample and equivalent exposure to the light. This resulted in much longer irradiation times (0.25–210 h) than were required for solution or slurry experiments. The solid samples were then extracted for 12 h in a specially designed microsoxlet extractor with benzene as a solvent; we found that recovery with benzene was always better than 90%, while other solvents, such as diethyl ether, dichloromethane, or *n*-hexane, led to recoveries in the 30–70% range. The extract was then analyzed by gas chromatography on a Perkin-Elmer 8320

(1) Issued as NRCC-29626.
(2) (a) Visiting scientist from Instituto de Quimica e Fisica de Sao Carlos, Brazil. (b) Visiting scientist from the University of Chile. (c) NRCC summer student.
(3) Casal, H. L.; Scaiano, J. C. *Can. J. Chem.* **1984**, *62*, 628.
(4) Casal, H. L.; Scaiano, J. C. *Can. J. Chem.* **1985**, *63*, 1308.
(5) Scaiano, J. C.; Casal, H. L.; Netto-Ferreira, J. C. *ACS Symp. Ser.* **1985**, *278*, 211.
(6) Wilkinson, F.; Willsher, C. J.; Casal, H. L.; Johnston, L. J.; Scaiano, J. C. *Can. J. Chem.* **1986**, *64*, 539.
(7) Turro, N. J.; Lei, X.; Cheng, C. C.; Corbin, D. R.; Abrams, L. *J. Am. Chem. Soc.* **1985**, *107*, 5824.
(8) Turro, N. J.; Cheng, C. C.; Lei, X. G.; Flanigen, E. M. *J. Am. Chem. Soc.* **1985**, *107*, 3739.
(9) Lei, X. G.; Doubleday, C. E., Jr.; Zimmt, M. B.; Turro, N. J. *J. Am. Chem. Soc.* **1986**, *108*, 2444.
(10) Turro, N. J. *Pure Appl. Chem.* **1986**, *58*, 1219.
(11) Corbin, D. R.; Eaton, D. F.; Ramamurthy, V. *J. Am. Chem. Soc.* **1988**, *110*, 4848.
(12) Turro, N. J.; Cheng, C. C.; Abrams, L.; Corbin, D. R. *J. Am. Chem. Soc.* **1987**, *109*, 2449.
(13) Hammond, G. S.; Saltiel, J.; Lamola, A. A.; Turro, N. J.; Bradshaw, J. S.; Cowan, D. O.; Counsell, R. C.; Vogt, V.; Dalton, C. *J. Am. Chem. Soc.* **1964**, *86*, 3197 and references therein.
(14) Flanigen, E. M.; Bennett, J. M.; Grose, R. W.; Cohen, J. P.; Patton, R. L.; Kirchner, R. M.; Smith, J. V. *Nature (London)* **1978**, *271*, 512.

0022-3263/89/1954-0259$01.50/0 Published 1989 by the American Chemical Society