benzenedimethanol and 0.143 g (1.28 mmol) of chlorobenzene in acetonitrile was added to 0.446 g (2.55 mmol) of dry silver acetate and 0.570 g (2.52 mmol) of NIS contained in a 10-mL flask. A condenser with a drying tube was connected to the flask. The mixture was stirred and heated at reflux in the dark (aluminum foil covered the flask) for 18 h. A 1-mL sample was removed and was filtered through a 5-μm filter with the use of a centrifuge. The sample was analyzed on an HPLC with chlorobenzene as an internal standard. The yields of lactone was 90% in 18 h. Silver iodide was recovered in 55% yield.

Acknowledgment. We are grateful to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for financial support of this work.

Registry No. 1, 110-63-4; 2, 516-12-1; 3, 563-63-3; 4, 96-48-0; 9 (hypoiodite deriv), 110590-71-1; 10, 4221-03-8; 11, 542-28-9; 12, 55549-01-4; 13, 1689-09-4; $HO(CH_2)_5OH$, 111-29-5; $HO(CH_2)_6OH$, 629-11-8; $2\text{-}HOCH_2C_6H_4CH_2OH$, 612-14-6; $I(CH_2)_3O_2CH$, 110590-72-2; ε-caprolactone, 502-44-3; phthalide, 87-41-2.

The Difference between Hydrogen and the Methyl Group as Electrophilic Centers in β-Elimination Reactions

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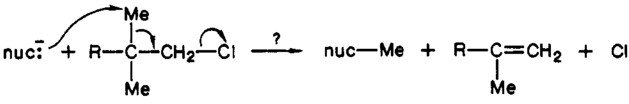
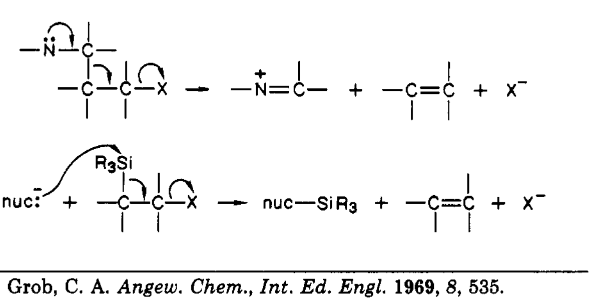
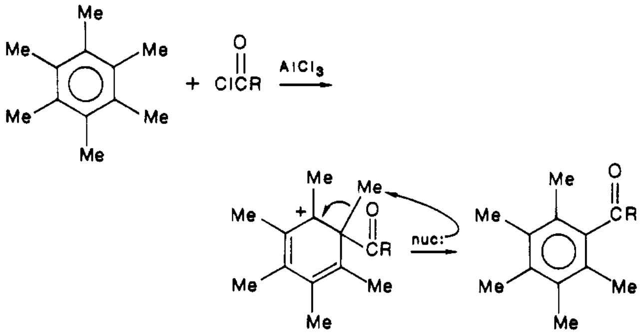
A methyl group often reacts like a hydrogen in organic reactions. When bonded to a metal and carrying a significant negative charge, each serves as a strong nucleophile (e.g., MeLi and LiH). When bonded to a halogen and carrying a significant positive charge, each serves as an electrophilic center (e.g., MeCl and HCl). When carrying no significant charge, each is usually unreactive as a nucleophile or electrophile. Important exceptions to this generalization occur, however, such as nucleophilic abstraction of a hydrogen from a carbon β to a leaving group in an elimination reaction. To our knowledge, however, no one has explored the possibility of a β-elimination, where a nucleophile abstracts a methyl group instead of a hydrogen.



1a, R = Ph
b, R = Me
c, R = 4-$NO_2C_6H_4$

Three comparable reactions nurtured our belief in the possibility of this untested elimination. The intramolecular electron flow of fragmentation reactions[1] runs parallel to the proposed elimination reaction, although here the nucleophilic nitrogen is already bonded to the carbon to be abstracted. Also the β eliminations where a nucleophile abstracts a trialkylsilyl group[2] proceed by the desired kind of electron flow. Finally, the second step of an anomalous Friedel–Crafts acylation[3] probably features a methyl abstraction to yield a carbon–carbon double bond.





We decided to test the novel elimination on three electrophiles expected to be favorably disposed toward the reaction. The first was 1-chloro-2-methyl-2-phenylpropane (neophyl chloride, **1a**), a candidate due to its lack of competing β hydrogens and the reluctance of its neophyl structure to undergo either S_N1 or S_N2 substitution. First, **1a** was mixed with a nucleophilic salt, either LiCl or NaCN, in DMF, a rate-enhancing, polar, aprotic solvent. After 22 h at 100 °C and a further 22 h at 125 °C, the NMR of the reaction mixtures showed no reaction. Finally, after a further 4 days at reflux (~153 °C), the NMR showed signs of reaction. Chloride nucleophile converted **1a** to 2-methyl-1-phenyl-1-propene. This unexceptional product doubtless resulted from a phenyl shift on the neophyl carbocation, followed by ordinary E1 elimination. On the other hand, cyanide, an extremely strong nucleophile in DMF,[4] left mostly starting material as well as a compound with no vinyl protons, probably the substitution product, 3-methyl-3-phenylbutanenitrile. With neither salt was any desired product, 2-phenyl-1-propene, observed.

Next, **1a** was combined with a nucleophilic amine, either morpholine or Bu_3N, as the solvent to increase the probability of collision between nucleophile and electrophile. The reaction mixtures were heated at 123–129 °C for 2 days. Although deep red colors developed, the NMR spectra showed only starting materials.

To avoid the unwanted phenyl shift of **1a**, an electrophile with only methyl groups in the β position, 1-chloro-2,2-dimethylpropane (neopentyl chloride, **1b**), was subjected to nucleophiles. After heating **1b** with LiCl or NaCN in DMF at 200 °C for 2 days in a sealed bomb, NMR showed only starting materials. Reaction was observed when **1b** was heated in morpholine at 200 °C for 3 days in the bomb. NMR indicated a solid product to be morpholine hydrochloride, while the liquid component appeared to contain the substitution product, *N*-neopentylmorpholine. But no sign of *N*-methylmorpholine, the product of a methyl abstraction, was observed.

Finally, the novel elimination was tried on the third electrophile, 1-chloro-2-methyl-2-(4-nitrophenyl)propane (**1c**). Its electron-withdrawing nitro group provides **1c** with two advantages over its analogue, **1a**: diminished tendency to undergo undesirable phenyl shift and somewhat diminished electron density (i.e. increased electrophilicity) at the methyl group to be abstracted. Yet after refluxing for 1 day, a mixture of **1c** and NaCN in DMF indicated no reaction by NMR. Refluxing a solution of **1c** in morpholine for 3 days allowed perhaps a little substitution of

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(1) Grob, C. A. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 535.

(2) Colvin, E. W. *Silicon in Organic Chemistry*; Butterworths: London, 1981; pp 141–164.

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(4) Parker, A. J. *Chem. Rev.* **1969**, *69*, 1.

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morpholine for chlorine, but no elimination.

Thus the sought methyl abstraction was not found for these three well-disposed electrophiles. Whether this novel reaction is viewed as a S_N2 reaction on the methyl group with an unusual carbon leaving group or as a E2 reaction with methyl abstraction, the conditions seemed strong enough to allow this reaction if it were kinetically feasible. Nor should thermodynamics have prevented reaction. For example, at 25 °C, enthalpy favors cyanide abstracting a methyl group from 1-chloropropane over cyanide abstracting hydrogen from chloroethane ($\Delta H^0 = -9.4$ vs -0.7 kcal/mol by heats of formation).

The reason for failed methyl abstraction is open to speculation. Either a hydrogen or a methyl group on a β carbon is sterically open to nucleophilic attack. Neither holds significant positive charge to attract a nucleophile. But a β hydrogen does have an advantage in being able to form a kind of hydrogen bond with the nucleophile in the transition state of a normal elimination reaction. In contrast, a methyl carbon cannot hydrogen bond and must rehybridize in its transition state. Such handicaps evidently prevent abstraction of a β-methyl group in elimination reactions even under otherwise favorable conditions. Probably the same handicaps deter strong nucleophiles, which can abstract alcohol hydrogens, from attacking ethers. Despite many similarities between the reactivities of hydrogen and a methyl group, another significant difference has now been established.

Experimental Section

DMF was purified by stirring with KOH for a few hours and then distilling from CaO onto 4A molecular sieves under aspirator vacuum. Morpholine was purified by stirring with $CaSO_4$ overnight and then fractionally distilling. Bu_3N was purified by stirring with KOH overnight and then distilling at 3 mmHg. LiCl and NaCN were dried in the oven. NMR spectra were recorded on a Varian EM360A proton spectrometer and are reported in δ units. The IR spectrum was recorded on a Perker-Elmer 1320 spectrometer.

Reaction of 1a with LiCl. A mixture of 3.37 g (20.0 mmol) of **1a**, 1.27 g (30.0 mmol) of LiCl, and 4.65 mL of DMF was refluxed for 4 days. NMR (DMF) δ 7.42 (br s, 5 H, Ar), 6.47 (br s, 1 H, HC=C), 2.15 (br s, 6 H, Me), very like the spectrum of authentic 2-methyl-1-phenyl-1-propene.

Reaction of 1a with NaCN. A mixture of 3.37 g (20.0 mmol) of **1a**, 0.98 g (20 mmol) of NaCN, and 4.65 mL of DMF was refluxed for 4 days. NMR (DMF) δ 7.39 (m, Ar), 1.47 (m, Me + CH_2), consistent with 3-methyl-3-phenylbutanenitrile; no vinyl protons; also peaks for starting materials.

Reaction of 1a with Morpholine or Bu_3N. A solution of 3.37 g (20.0 mmol) of **1a** and either 3.48 g (40.0 mmol) of morpholine or 6.19 g (33.4 mmol) of Bu_3N was heated at 123-129 °C for 2 days. NMR showed no reaction.

Reaction of 1b with LiCl or NaCN. A mixture of 2.66 g (25.0 mmol) of **1b** and either 2.00 g (47.2 mmol) of LiCl or 0.50 g (10 mmol) of NaCN in 11.62 mL of DMF was heated at 200 °C in a sealed bomb for 2 days. NMR showed no reactions.

Reaction of 1b with Morpholine. A solution of 5.32 g (50.0 mmol) of **1b** and 8.72 g (100 mmol) of morpholine was heated at 200 °C in a sealed bomb for 3 days. A reddish brown liquid and a white solid resulted: NMR (of liquid) δ 3.80 (t, 4 H, H_2CO), 2.67 (t, 4 H, $OCCH_2N$), 2.26 (s, 2 H, neopentyl CH_2), 1.13 (s, 9 H, Me), consistent with *N*-neopentylmorpholine; also peaks for starting materials.

1-Chloro-2-methyl-2-(4-nitrophenyl)propane (1c). A mixture of 1.69 g (10.0 mmol) of **1a**, 1.27 mL (19.9 mmol) of 70% HNO_3, 2.21 mL (40.0 mmol) of concentrated H_2SO_4, and 6 mL of CH_2Cl_2 was stirred for 1 h. The organic layer was washed with saturated $NaHCO_3$ and NaCl solutions, dried with Na_2SO_4, and concentrated under vacuum. From 1.96 g of yellowish liquid crude **1c** was eluted at 1.0-g aliquot through 25 g of a silica gel column with 0-15% ether-hexane to yield 0.55 g of white **1c**: mp 29-33 °C; IR (melt) 1510 and 1340 cm^{-1} (NO_2); NMR ($CDCl_3$) δ 7.86 (2 d, 4 H, Ar), 3.66 (s, 2 H, CH_2), 1.46 (s, 6 H, Me), consistent with **1c**.

Reaction of 1c with NaCN. A mixture of 0.213 g (1.00 mmol) of **1c**, 0.196 g (4.00 mmol) of NaCN, and 1.0 mL of DMF was refluxed for 1 day. NMR showed no reaction.

Reaction of 1c with Morpholine. A solution of 0.213 g (0.997 mmol) of **1c** and 0.90 g (10 mmol) of morpholine was refluxed for 3 days. NMR δ 2.64, perhaps a little substitution product; no vinyl protons; also peaks for starting materials.

Acknowledgment. We thank the Research Corporation and the SUNY Research Foundation for financial support of this research and Professors A. Miller, J. R. Mohrig, C. D. Ritchie, and W. H. Saunders for helpful discussions.

Registry No. 1a, 515-40-2; 1b, 753-89-9; 1c, 99359-77-0; 2-methyl-1-phenyl-1-propene, 768-49-0; 3-methyl-3-phenylbutanenitrile, 17684-33-2; *N*-neopentylmorpholine, 67061-35-2.

Relative Ease of Transient Acyl Imine Formation via Selenoxide, Sulfoxide, and Sulfone β N-H Elimination. A Feasibility Study on the Preparation of Novel Peptide Analogues

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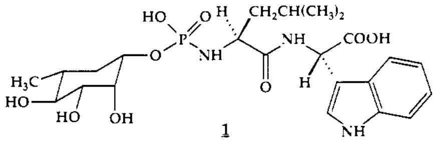
Many biomedically important naturally occurring and synthetic protease inhibitors have tetrahedral phosphorus functional groups as transition-state analogues or reactive-intermediate analogues. The microbial metabolite phosphoramidon **1**, long known as a potent competitive inhibitor of the bacterial zinc endopeptidase thermolysin,[1] has recently been shown to produce analgesia in rats, presumably via inhibition of the degradation of endogenous opioid peptides by the zinc protease enkephalinase.[2] Synthetic **2** and related compounds inhibit the human zinc peptidase neutrophil collagenase, which is believed to cause pathological connective tissue destruction in rheumatoid arthritis.[3] Synthetic **3** and related compounds inhibit the aspartic protease pepsin,[4] a model enzyme for the human blood pressure regulating enzyme renin.



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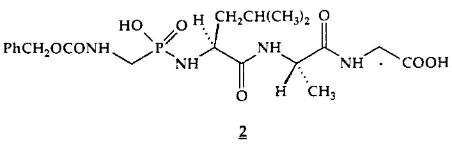

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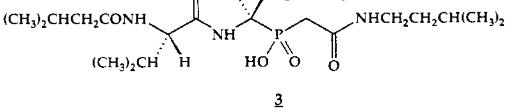

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It is reasonable to expect that tetrahedral selenoxide, sulfoxide, and sulfone functional groups should also possess

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[†] Fellow of the Alfred P. Sloan Foundation, 1987-1989.