program and correlation coefficients of greater than 0.995 were obtained. Results are listed in Table I.

Elastase activity depends upon a functional group with a pK of 6.5–6.85 (His-57)[13] and although the enzyme possesses only slight proteolytic activity at pH 5.0, most inhibition experiments were performed at this pH since the rates of reaction were too rapid to follow at higher pH values even when only a tenfold excess of inhibitor was employed. Our results clearly show that the rate of inhibition of elastase is markedly affected by the chain length of the chloromethyl ketone, Ac-Ala-Ala-Pro-AlaCH$_2$Cl being the most effective inhibitor. Inhibitors possessing a P_4 residue[14] are 8–34 times faster than those without. Simple substrate analogs such as Tos-AlaCH$_2$Cl and Tos-ValCH$_2$Cl are incapable of inhibiting the enzyme.[5,6] The rate of hydrolysis of simple peptide substrates by elastase is also markedly accelerated when the substrate contains a P_4 residue to interact with the S_4 binding subsite of the enzyme.[10] In contrast to the results obtained with substrates, where approximately a 25-fold rate acceleration is observed, a phenylalanyl residue in P_2 causes a slight decrease in the rate of inhibition. A leucyl or a prolyl residue in the P_2 position of an inhibitor accelerates the inhibition rate. An analogous effect with leucine has been observed in the rates of inhibition of the homologous serine protease chymotrypsin by a series of peptide chloromethyl ketones.[15] A more detailed discussion of the interactions between these peptide chloromethyl ketones and elastase must await the X-ray structure determination of an inhibited elastase derivative.

In addition to porcine elastase, several of the above compounds inhibit a human pancreatic enzyme which hydrolyzes BOC-Ala-ONP but not elastin.[16] The digestion of human lung tissue and rat aorta by pancreatic porcine elastase or by a human polymorphonuclear leukocyte elastase is completely inhibited by Ac-Ala-Ala-AlaCH$_2$Cl.[17] Also the increased agglutinability of mouse fibroblasts induced by treatment with a leukocyte lysosomal protease was inhibited by Ac-Ala·Ala-Pro-AlaCH$_2$Cl.[18]

The alanyl chloromethyl ketones thus far investigated appear to have a high specificity for elastolytic enzymes. Inhibition of trypsin by these compounds has not been observed. Several compounds (Ac-Ala-Gly-AlaCH$_2$Cl and Z-Gly-Leu-AlaCH$_2$Cl) inhibit bovine chymotrypsin, but the rates are less than 10% of those observed with elastase.[19] These inhibitors are therefore useful tools for studying the catalytic site, extended binding region, and biological function of elastase and related proteases.

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Stable Uranium(IV) Alkyl and Aryl Complexes

Sir:

Beginning with the synthesis of "uranocene,"[1] there has been a renaissance of interest in organoactinide chemistry.[2] Such questions as covalency, the involvement of 5f orbitals in chemical bonding, and chemical similarities to transition metals are of fundamental importance in actinide chemistry. To date, organouranium molecules are only known for polyhapto, π-bonding ligand systems, *viz.* h^5-C_5H_5 (cyclopentadienyl),[2] h^5-C_9H_7 (indenyl),[3] h^3-C_3H_5 (allyl),[2] h^8-C_8H_8 (cyclooctatetraene),[2,4] and h^6-C_6H_6 (arene),[5] with alkyl-substituted ligands included. No well-defined σ-bonded organometallics have yet been reported for uranium (or any actinide) in the chemical literature.[6] We report here the first synthesis of a series of such compounds, $(h^5\text{-}C_5H_5)_3UR$, and some of the more interesting properties of these new molecules.

The reaction of $(h^5\text{-}C_5H_5)_3UCl$[7] with organolithium or Grignard reagents produces the extremely air-sensitive alkyl and aryl compounds in high yield (60–80%).

$$(h^5\text{-}C_5H_5)_3UCl + RLi \longrightarrow (h^5\text{-}C_5H_5)_3U\text{-}R + LiCl$$

$$(h^5\text{-}C_5H_5)_3UCl + RMgX \longrightarrow (h^5\text{-}C_5H_5)_3U\text{-}R + MgXCl$$

Ia, R = CH_3
b, R = n-C_4H_9
c, R = allyl
Id, R = neopentyl
e, R = C_6F_5
f, R = i-C_3H_7

Purification can be achieved by hydrocarbon (toluene–hexane) extraction and crystallization (−78°).[8] Nmr

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Table I

Compd	Color	Nmr[a,b] (toluene solution)
Ia	Yellow-brown	+10.0 (15 H), +202 (3 H)
Ib	Dark red-brown	+10.3 (15 H), +18.7 (3 H), +27.6 (2 H), +33.6 (2 H), +195 (2 H)
Ic	Dark brown	+10.0 (15 H), +38.2 (1 H), +126 (4 H) (+25°) +13.1 (15 H), +41.0 (1 H), +57.5 (1 H), +60.9 (1 H), +334 (2 H) (−90°)
Id	Dark red-brown	+11.6 (15 H), +22.1 (3 H), +186 (2 H)
Ie	Dark brown	+10.9 (15 H), +88.7 (2 F), 99.1 (2 F), +115.5 (1 F)
If	Dark red-brown	+10.9 (15 H), +19.3 (6 H), +190 (1 H)

[a] Pmr data in parts per million to high field of internal benzene. ^{19}F data in parts per million to high field of internal $C_6H_5CF_3$. [b] All data at +25° except where indicated.

data (Table I), which include some of the largest chemical shifts yet observed for uranium(IV) organometallics,[2] are in good accord with the above formulation. The allyl molecule is fluxional with room temperature and above, nmr spectra approaching an A_4X pattern, while the lower temperature spectra reveal collapse of the high-field peak and eventual freezing out of the *monohapto*allyl[9,10] A_2BCD pattern at −85°. Infrared spectra clearly indicate that the cyclopentadienyl rings in all molecules are π bonded.[11]

The nature of the uranium–carbon σ bond is, of course, the feature of greatest interest. In this connection, we find that these molecules all possess considerable thermal stability. In the solid state under nitrogen, there is no noticeable decomposition after days at room temperature. In toluene solution (0.054 *M*), all molecules decompose at nearly the same rate, with half-lives of 20–96 hr at 72°; at 100°, 15 hr are required to completely destroy Ib. The narrow spectrum of thermal stability we observe deviates considerably from most transition metal systems, where fluorine substitution[12,13] or prevention of β-hydrogen abstraction[13,14] greatly increases resistance to thermolysis, and this apparently anomalous behavior has prompted some mechanistic investigation. The major organic decomposition product of Ib is *n*-butane (92 ± 3% yield by glpc), with trace amounts of 1-butene (<2%) and *n*-octane (<1%) also detected. This result (especially the near absence of 1-butene) can be contrasted with a thermally less stable, well-studied *n*-butylcopper(I) system[15] where *ca.* 1:1 butane–butene was produced, suggesting that β-hydrogen elimination was operative, *i.e.*

$$M\text{–}CH_2CH_2R \longrightarrow M\text{–}H + CH_2{=}CHR$$

$$M\text{–}H + M\text{–}CH_2CH_2R \longrightarrow 2M + CH_3CH_2R$$

The uranium(IV) organometallics, however, appear to resist β elimination, and this apparently enhances the thermal stability. A homolytic, free-radical bond scission is the most reasonable alternative pathway.[13,16,17]

The polarity of the uranium–carbon bond was also investigated. All compounds react instantly with methanol, producing as the major product the known compound, $(C_5H_5)_3UOCH_3$.[19] No reaction was observed when it was attempted to bring about nucleophilic addition of $(C_5H_5)_3UCH_3$ to acetone. It is clear that uranium–carbon σ bonds constitute a new facet of organoactinide chemistry, and this area is under continuing exploration.[20]

Acknowledgments. We are grateful to the National Science Foundation (GP-30623X) and the Research Corporation for support of this work and to the staff of the Chemistry Department Analytical Services Laboratory for assistance with several measurements.

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On Making Corrections for Donor Nonideality on Molecular Complex Equilibria

Sir:

The authors of a recent publication[1] questioned the validity of equilibrium constants evaluated by spectrophotometric means for the 1:1 association between a Lewis acid A and a Lewis base D to form the adduct AD (eq 1). They objected to expressing the equilib-

$$A + D \rightleftharpoons AD \qquad (1)$$

rium constant for eq 1 in terms of concentration, for the various species, instead of the activities. As evidence for their proposal that activities should be used instead of concentrations, they investigated the system caffeine–benzene in CCl_4 solvent using nmr for determining K, the equilibrium constant, and Δ_{AD}, defined as the difference in chemical shift between free and fully complexed caffeine.

Since Δ_{AD} is concentration independent, data evaluated to solve for Δ_{AD} and K should give the same value for Δ_{AD} regardless of the concentration scale used (*i.e.*, *molal* or *mole fraction*). Since they found that Δ_{AD} evaluated when the initial donor concentration, D^0, was expressed in molal units was significantly different than when D^0 was expressed in mole fraction units, they con-

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