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corresponded to the $[M + 11H]^{11+}$ and $[M + 10H]^{10+}$ protonation states of the native (i.e., homodimeric) enzyme–inhibitor complex. The data are shown in Figures 1 and 2. The ternary complex had a mass of 22 345 Da, as expected for 2 HIV PR subunits and JG365 ($C_{1021}H_{1672}N_{270}O_{281}S_4$ calculated monoisotopic mass 22340.4, average mass 22354.4). By raising the declustering voltage at the ion sampling orifice, it was possible to dissociate the complex either partially (Figure 2b), thus observing both the ternary complex and monomeric HIV PR, or entirely, so that only the enzyme monomer was observed (Figure 2c).

Observation of the ternary complex is direct proof of 1:1 stoichiometry between the dimeric enzyme and inhibitor and is consistent with crystallographic[12] and kinetic[17] data. Interestingly, the unique internal water molecule observed in the crystal structure of this[12] and other HIV PR–inhibitor complexes[11,13,19,20] was not observed. This is surprising given that this water molecule is internal to the folded structure and appears to be tightly coordinated, with two hydrogen bonds to the amide backbone of the enzyme and two to the inhibitor.

The demonstration that noncovalent macromolecular complexes can be directly observed will extend the applications of mass spectrometry to the study of protein–protein, protein–DNA, receptor–ligand, enzyme–substrate, and enzyme–inhibitor macromolecular complexes. Dissociation of such complexes by raising the declustering voltage at the ion sampling orifice will make possible the facile distinction between covalent and noncovalent complexes.

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(19) Fitzgerald, P. M. D.; McKeever, B. M.; VanMiddlesworth, J. F.; Springer, J. P.; Heimbach, J. C.; Leu, C. T.; Herber, W. K.; Dixon, R. A. F.; Darke, P. L. *J. Biol. Chem.* **1990**, *265*, 14209-14219.

(20) Erickson, J.; Neidhart, D. J.; VanDrie, J.; Kempf, D. J.; Wang, X. C.; Norbeck, D. W.; Plattner, J. J.; Rittenbouse, J. W.; Turon, M.; Wideburg, N.; Kohlbrenner, W. E.; Simmer, R.; Helfrich, R.; Paul, D. A.; Knigge, M. *Science* **1990**, *249*, 527-533.

New Trialkylsilyl Enol Ether Chemistry. Conjugate Additions without the Enone

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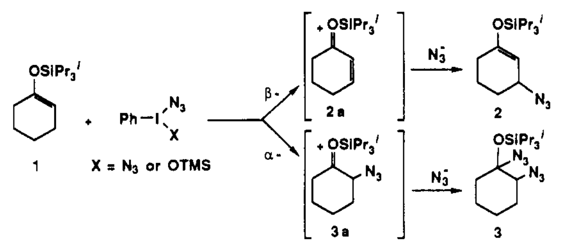
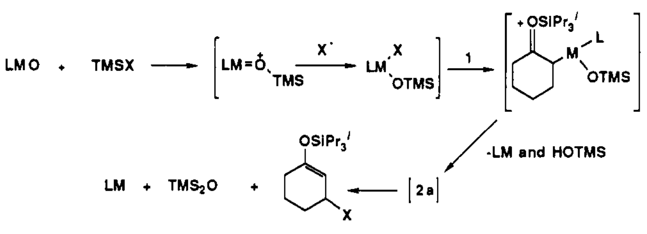
Triisopropylsilyl (TIPS) enol ethers undergo electrophilic substitution chemistry and retain the triisopropylsilyl group.[1] The normal desilylation that is observed in the case of trimethylsilyl enol ethers is prevented by the bulky isopropyl ligands. While attempting to introduce α-amino functionality into TIPS enol ethers, we examined a number of potential electrophilic nitrogen reagents.[2] Much to our surprise, it was found that treatment of a variety of TIPS enol ethers with Me_3SiN_3 (2.4 equiv)/PhIO (1.2 equiv)/CH_2Cl_2 at −15 to −18 °C gave excellent yields of the *β-azido adduct* **2** rather than the expected (normal) α-azido adduct **3** (Scheme I).[3] The β-azido adduct most probably arises from the enonium ion **2a** and the α-diazide from the onium ion **3a**. This new transformation appears to be a member of a general unexplored class of reactions that can be represented by Scheme II.[4]

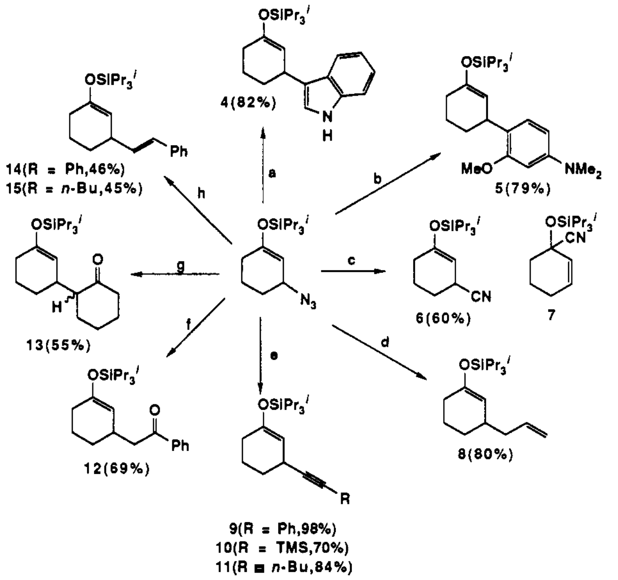
Scheme I



Scheme II



Scheme III[a]



[a] (a) Indole/Me_3Al/CH_2Cl_2, −70 °C. (b) *m*-$MeOC_6H_4NMe_2$/Me_2AlCl/hexane, 25 °C. (c) Et_2AlCN/THF, reflux. (d) Allyltri-*n*-butylstannane/Me_2AlCl/hexane, −70 °C. (e) RCCH/*n*-BuLi/Me_2AlCl/hexane, 25 °C. (f) Acetophenone TMS enol ether/Me_2AlCl/hexanes, 25 °C. (g) Cyclohexanone TMS enol ether/Me_2AlCl/hexanes, 25 °C. (h) RCCH/Cp_2ZrHCl/Me_2AlCl/hexane, 25 °C.

To examine the trapping of the enonium ion **2a** with nucleophiles other than azide ion, we examined the response of the β-azido adduct **2** to carbon nucleophiles in the presence of Lewis acids. The preliminary results are shown in Scheme III.

Treatment of **2** with indole (2 equiv)/Me_3Al (2 equiv)/CH_2Cl_2 at −70 °C gave the 3-substituted derivative **4** (82%). Similarly, the presumed enonium ion **2a** could be trapped with *m*-$MeOC_6H_4NMe_2$ to give **5** (79%). The Nagata reagent[5] in dichloromethane gave a mixture of **6** and **7** (2:1), whereas the same reaction in THF at reflux gave only **6** (60%). While the addition

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(1) Magnus, P.; Mugrage, B. *J. Am. Chem. Soc.* **1990**, *112*, 462.

(2) Magnus, P.; Lacour, J.; Bauta, W.; Mugrage, B.; Lynch, V. *J. Chem. Soc., Chem. Commun.* **1991**, 1362. Magnus, P.; Barth, L. *Tetrahedron Lett.* In press. Unpublished results from this lab.

(3) Magnus, P.; Lacour, J. *J. Am. Chem. Soc.* **1992**, *114*, 767.

(4) Treatment of **1** with *n*-$Bu_4N^+IO_4^-$/$TMSN_3/CH_2Cl_2$ gave **2** and **3** (1:1). B. Kersten, University of Texas at Austin.

(5) Nagata, W.; Yoshioka, M.; Hirai, S. *J. Am. Chem. Soc.* **1972**, *94*, 4635. Nagata, W.; Yoshioka, M.; Murakami, M. *J. Am. Chem. Soc.* **1972**, *94*, 4644. Nagata, W.; Yoshioka, M.; Terasawa, T. *J. Am. Chem. Soc.* **1972**, *94*, 4672. Nagata, W.; Yoshioka, M. *Org. React.* **1977**, *25*, 255. Utimoto, K.; Obayashi, M.; Shishiyama, Y.; Inoue, M.; Nozaki, H. *Tetrahedron Lett.* **1980**, *21*, 3389.

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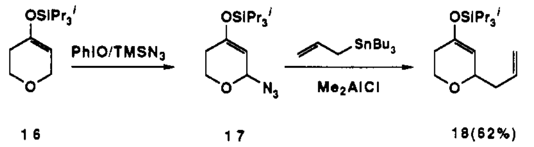
Scheme IV



of allyltri-*n*-butylstannane to enones is known,[6] the regiospecific trapping of the enolate with silylating agents, particularly TIPSCl or TIPSOTf, is a low-yielding reaction.[7] Consequently, the formation of **8** (80%) is noteworthy. Acetylenic anions are nontransferable ligands in organocuprate chemistry, and indirect methods have been developed to make β-acetylenic ketones.[8] Recently Kim[9] has reported the trialkylsilyl triflate promoted addition of alkynylzinc to enones. The enonium ion **2a** can be trapped with terminal acetylenes by treatment with *n*-BuLi followed by Me_2AlCl to give excellent yields of **9**, **10**, and **11** (98, 70, and 84%, respectively). Trimethylsilyl enol ethers trap **2a** to give the mixed TIPS enol ether-ketones **12** and **13** (3:1 diastereomers).[10] This transformation should find useful applications since it allows direct differentiation between the two ketone functionalities. Hydrozirconation of phenylacetylene followed by Me_2AlCl and addition of **2** gave the styrene **14** (46%).[11]

It is possible to perform a one-pot conversion of a TIPS enol ether into its β-carbon-substituted derivative. This is illustrated in Scheme IV for the conversion of the 4-pyranone TIPS enol ether **16** into **17** (not isolated) and for the direct treatment with allyltri-*n*-butylstannane/Me_2AlCl to give the β-allyl adduct **18** (62%).

This simple and versatile new methodology should find many applications in both the individual reactions and overall strategies of organic synthesis.

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Supplementary Material Available: Listings of spectral details for compounds **4–15** and **18** (11 pages). Ordering information is given on any current masthead page.

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(6) Hosomi, A.; Iguchi, H.; Endo, M.; Sakurai, H. *Chem. Lett.* **1979**, 977. Mobilio, D.; De Lange, B. *Tetrahedron Lett.* **1987**, *28*, 1483–86. Lithium diallylcuprate: House, H. O.; Fisher, W. F. *J. Org. Chem.* **1969**, *34*, 3615.

(7) Treatment of 3-methylcyclopentenone with Me_2CuLi followed by TIPSOTf/Et_3N/HMPA gave only a 10% yield of the derived TIPS enol ether. Mugrage, B., unpublished results from this lab.

(8) House, H. O.; Fisher, W. F. *J. Org. Chem.* **1969**, *34*, 3615. Corey, E. J.; Beames, D. J. *J. Am. Chem. Soc.* **1972**, *94*, 7210. Pappo, P. W.; Dajanni, E. Z.; Bruhn, M. S.; Brown, H. C.; Palmer, J. R.; Pappo, R. *Tetrahedron Lett.* **1975**, *16*, 4217. Sinclair, J. A.; Molander, G. A.; Brown, H. C. *J. Am. Chem. Soc.* **1977**, *99*, 954. Corey, E. J.; Wollenberg, R. H. *J. Am. Chem. Soc.* **1977**, *99*, 8045. Hooz, J.; Layton, R. B. *J. Am. Chem. Soc.* **1971**, *93*, 7320. Hansen, R. T.; Carr, D. B.; Schwartz, J. *J. Am. Chem. Soc.* **1978**, *100*, 2245.

(9) Kim, S.; Lee, J. M. *Tetrahedron Lett.* **1990**, *31*, 7627.

(10) Carbocupration: Normant, J. F.; Alexakis, A. *Synthesis* **1981**, 841. Lipschutz, B. H. *Synthesis* **1987**, 325. Foulon, J. P.; Bourgain-Commerçon, M.; Normant, J. F. *Tetrahedron* **1986**, *42*, 1389. Hydroalumination: Whitney, C. C.; Zweifel, G. *J. Am. Chem. Soc.* **1967**, *89*, 2753. Negishi, E.; Takahashi, T. *Synthesis* **1988**, 1. Negishi, E. *Pure Appl. Chem.* **1981**, *53*, 2333. Hydrozirconation: Schwartz, J.; Labinger, J. A. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 333. Carr, B. D.; Schwartz, J. *J. Am. Chem. Soc.* **1977**, *99*, 639. Yoshifuji, M.; Loots, M. J.; Schwartz, J. *Tetrahedron Lett.* **1977**, *15*, 1303. Loots, M. J.; Schwartz, J. *J. Am. Chem. Soc.* **1977**, *99*, 8045. Van Horn, D. E.; Negishi, E. *J. Am. Chem. Soc.* **1978**, *100*, 2252. Negishi, E.; Van Horn, D. E.; Yoshida, T. J. *J. Am. Chem. Soc.* **1985**, *107*, 6639. Ireland, R. E.; Wipf, P. *J. Org. Chem.* **1990**, *55*, 1425. Lipschutz, B. H.; Ellsworth, E. L. *J. Am. Chem. Soc.* **1990**, *112*, 7440.

(11) 1,5-Diketones: Narasaka, K.; Soai, K.; Mukaiyama, T. *Chem. Lett.* **1974**, 1223. Narasaka, K.; Soai, K.; Aikawa, K.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 779. Saigo, K.; Osaki, M.; Mukaiyama, T. *Chem. Lett.* **1976**, 163. For information on the stereoselection, see: Heathcock, C.; Norman, M. H.; Uehling, D. E. *J. Am. Chem. Soc.* **1985**, *107*, 2797. Heathcock, C.; Uehling, D. E. *J. Org. Chem.* **1986**, *51*, 279. CsF-induced: Boyer, J.; Corriu, R. J. P.; Perz, R.; Reye, C. *J. Organomet. Chem. Commun.* **1980**, *184*, 157. Boyer, J.; Corriu, R. J. P.; Perz, R.; Reye, C. *J. Chem. Soc., Chem. Commun.* **1981**, 122. Boyer, J.; Corriu, R. J. P.; Perz, R.; Reye, C. *Tetrahedron* **1983**, *39*, 117. Montmorillonite clay: Kawai, M.; Onaka, M.; Izumi, Y. *J. Chem. Soc., Chem. Commun.* **1987**, 1203. $BF_3 \cdot OEt_2$: Duhamel, P.; Hennequin, L.; Poirier, N.; Poirier, J.-M. *Tetrahedron Lett.* **1985**, *26*, 6201. Trityl perchlorate: Kobayashi, S.; Murakami, M.; Mukayaima, T. *Chem. Lett.* **1985**, 953. Mukaiyama, T.; Tamura, M.; Kobayashi, S. *Chem. Lett.* **1986**, 1017. TBDMSO-pyrylium salt: Iwasaki, H.; Kume, T.; Yamamoto, Y.; Akiba, K. *Tetrahedron Lett.* **1987**, *28*, 6355. Mukaiyama, T.; Tamura, M.; Kobayashi, S. *Chem. Lett.* **1986**, 1017.

Unusual Electrochemical Properties of the Higher Fullerene, Chiral C_{76}

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Approximately a year ago, it was discovered that the fullerenes C_{60} and C_{70} have an exceptionally high electron affinity. Two,[1a] three,[1b,c] four,[1d] and five reversible reduction steps[1e] have been recorded for C_{60}, and the two fullerenes were found to have essentially the same redox properties.[1b] No *reversible* oxidation waves were observed in the cyclic voltammograms of both carbon spheres. An explanation for the high electron affinity in terms of pyracyclene units was proposed and shown to be a good model for predicting the chemical reactivity of C_{60}.[1b] Recently, some of us reported the isolation in pure form and structural characterization of three higher fullerenes, chiral C_{76}[2] (Figure 1) and the two isomers C_{2v}-C_{78} and D_3-C_{78}.[3] The onset of the electronic absorption by these compounds occurs at much lower energy than the optical absorption onset measured for C_{60} and C_{70}, and the result of calculations on the electronic structure of the higher fullerenes was used to predict that C_{76} would be both a better donor and a better acceptor than C_{60}.[2,4] Since milligram quantities of the title fullerene have become available in the recent past, it was imperative to determine its electrochemical properties by cyclic voltammetry (CV).

For the isolation of the higher fullerenes, C_{60} and C_{70} were first removed by two chromatographic runs on neutral alumina with hexanes/toluene (95:5) as the eluent. The higher fullerene fraction was subsequently separated in three sequential runs on a 25 × 2.5 cm Vydac 201-TP C18 reversed-phase column with acetonitrile/toluene (50:50) as the eluent, giving pure C_{76}, C_{2v}-C_{78}, and D_3-C_{78} as well as a C_{84} fraction containing two isomers.[3,5-7]

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(1) (a) Haufler, R. E.; Conceicao, J.; Chibante, L. P. F.; Chai, Y.; Byrne, N. E.; Flanagan, S.; Haley, M. M.; O'Brien, S. C.; Pan, C.; Xiao, Z.; Billups, W. E.; Ciufolini, M. A.; Hauge, R. H.; Margrave, J. L.; Wilson, L. J.; Curl, R. F.; Smalley, R. E. *J. Phys. Chem.* **1990**, *94*, 8634–8636. (b) Allemand, P. M.; Koch, A.; Wudl, F.; Rubin, Y.; Diederich, F.; Alvarez, M. M.; Anz, S. J.; Whetten, R. L. *J. Am. Chem. Soc.* **1991**, *113*, 1050–1051. (c) Cox, D. M.; Bahal, S.; Disko, M.; Gorun, S. M.; Greaney, M.; Hsu, C. S.; Kollin, E. B.; Millar, J.; Robbins, J.; Sherwood, R. D.; Tindall, P. *J. Am. Chem. Soc.* **1991**, *113*, 2940–2944. (d) Dubois, D.; Kadish, K. M.; Flanagan, S.; Haufler, R. E.; Chibante, L. P. F.; Wilson, L. J. *J. Am. Chem. Soc.* **1991**, *113*, 4364–4366. (e) Dubois, D.; Kadish, K. M.; Flanagan, S.; Wilson, L. J. *J. Am. Chem. Soc.* **1991**, *113*, 7773–7774.

(2) Ettl, R.; Chao, I.; Diederich, F.; Whetten, R. L. *Nature* (*London*) **1991**, *353*, 149–153.

(3) Diederich, F.; Whetten, R. L.; Thilgen, C.; Ettl, R.; Chao, I.; Alvarez, M. M. *Science* (*Washington, D.C.*) **1991**, *254*, 1768–1770.

(4) Cheng, H.-P.; Whetten, R. L. *Chem. Phys. Lett.*, in press. See also: Manolopoulos, D. E. *J. Chem. Soc., Faraday Trans.* **1991**, *87*, 2861–2862.

(5) Diederich, F.; Whetten, R. L. *Acc. Chem. Res.* **1992**, *25*, 119–126.

(6) Vydac C18 reversed-phase column: The Separations Group, 17434 Mojave St., Hesperia, CA 92345.