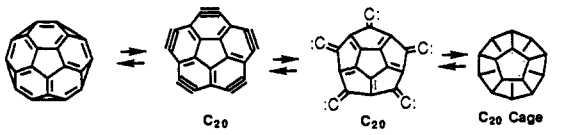
in this reaction generates the same polycyclic aromatics with H replaced by D in the case of D_2O. When CH_3OD is used as a trap, the products contain both D and H with H predominating as expected from a consideration of homolytic bond strengths.

The relationship between H donor concentration and yields is displayed graphically in Figure 1. Since compounds **4** and **5** contain remnants of the ring skeletons found in C_{60}, it is tempting to postulate that the decadehydro derivatives of these compounds are intermediates on the way to the fullerenes and are trapped by H abstraction. The data in Figure 1, which show an increase in trapping products with a corresponding decrease in C_{60} as H donor concentration is increased, are consistent with this hypothesis. A mechanism for the conversion of a C_{16} fragment, corresponding to **4**, to the fullerenes by a series of C_2 additions is proposed in Scheme I. Ring closure and cyclization of a C_{16} chain under the energetic conditions of fullerene formation could lead to dehydrofluoranthrene, **7**. Subsequent additions of two C_2 molecules to the free valences in **7** would generate the dehydrocorannulene, **8**. Stepwise addition of molecular C_2 then builds up the carbon clusters, eventually resulting in the fullerenes. In the steps leading from C_{16} to C_{50}, the growing carbon cluster adds to C_2 in a 1,2 fashion always generating intermediates with 10 free valences or five benzyne units. Once C_{50} is reached, continued addition to C_2 in a 1,2 fashion generates open C_{60}, **9**, which could rearrange to **10**, a C_{60} with five cyclopentadienylidene carbenes.[6] Cyclization of **10** yields fullerene-60. Alternately, C_{50} could add to C_2 molecules in a 1,1 fashion generating **10** directly. Addition of more C_2 molecules to **9** would lead to fullerene-70 or to tubules.[8]

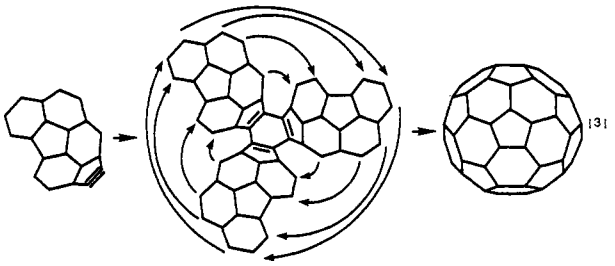
Smalley[2g] has proposed a "pentagon road" route to C_{60} in which carbon sheets with as many nonadjacent pentagons as possible reduce the number of dangling bonds to 10 during a large portion of the cluster buildup. The mechanism in Scheme I, which also involves intermediates with 10 free valences, may represent a route to the fullerenes along the "pentagon road". This mechanism, in which clusters grow by the addition of C_2 molecules, builds up the carbon clusters in even-numbered units, as is observed in mass spectral studies of clusters arising from laser-evaporated graphite.[9,10]

That the trapping experiments do not show C_nH_{10} with $n > 18$ may be due to the fact that once C_{20} is reached, free valences may be satisfied by formation of cages which are not trapped (eq 2).[11]



[2]

An interesting alternative explanation for our failure to trap clusters above C_{18} is a rapid trimerization of a C_{20} to fullerene-60 (eq 3). Although such a mechanism is not consistent with mass spectral studies of laser-evaporated graphite, C_{30} has been observed to dimerize to C_{60} in the gas phase,[12] and it seems possible that



[3]

a trimerization may play a role when C_{60} is generated in an arc.

These investigations implicate a mechanism of fullerene formation in which linear, monocyclic, and polycyclic carbon clusters precede fullerene synthesis.[13]

Acknowledgment. Support of this work through National Science Foundation Grants CHE-9013240 and CHE-9101252 is gratefully acknowledged.

(6) The rearrangement of **9** to **10** is an example of the benzyne to cyclopentadienylidene carbene rearrangement which has been calculated to be endothermic by 31 kcal/mol.[7] In the case of fullerene formation, this endothermicity would be compensated by cage formation.

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$\psi[PO_2^-CH_2N^+]$, a New Amide Bond Replacement: Potent, Slow-Binding Inhibition of the HIV Protease

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The design and synthesis of peptidomimetic enzyme inhibitors continue to be active areas of research. Such compounds have proven useful in elucidating mechanisms of catalysis and as therapeutic agents.[1] The discovery that the human immunodeficiency virus encodes an aspartic protease (HIV PR) vital for its propagation has brought this protein under intense scrutiny.[2,3] In this regard, the development of compounds which inhibit the HIV PR has been particularly rapid.[4]

It seemed rational that an effective modification of the phosphonamidate structure **1**, well-known in protease inhibition,[5] would be to include additional features along the reaction coordinate for amide hydrolysis. The insertion of a methylene spacer between phosphorus and nitrogen produces the nonhydrolyzable moiety **2**, which is likely a zwitterion near physiological pH. This construct could be representative of a late transition state/early

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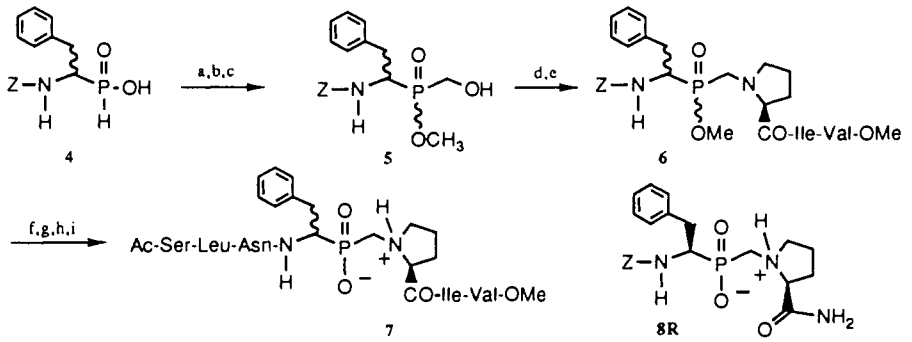
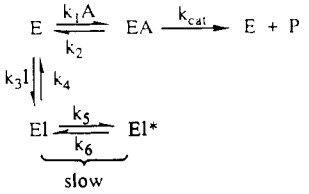
Scheme I[a]



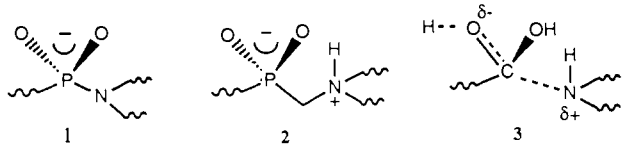
4 5 6 7 8R

[a] Reagents and conditions: (a) TMS-Cl, Et_3N, CH_2Cl_2, 5 °C, 3 h; (b) CH_2O, 3 h; (c) $(CH_3O)_3P$, 90 °C, 3 h, (45%); (d) CF_3SO_2Cl, DMAP, Et_3N, CH_2Cl_2, −50 °C, 3 h; (e) H-Pro-Ile-Val-OMe, THF, 3 h, (65%); (f) H_2, Pd/C, MeOH/ethyl acetate, 3 h; (g) Ac-Ser(Bzl)-Leu-Asn-OH, EDC, HOBT, ethyl acetate/DMF, 5 °C, 24 h, (75%); (h) H_2, $Pd(OH)_2$, MeOH/acetic acid, 16 h, (45%); (i) *tert*-butylamine, 45 °C, 24 h, (25%).

Scheme II



product formation for amide bond cleavage in mimicking both the tetrahedral hydrate and departing amine, **3**. Its incorporation into a peptide backbone affords what we term an "exploding transition-state analogue".



1 2 3

In analogy with the hydroxyethylamine surrogate utilized by Rich et. al.,[6] the scissile P_1–P_1' bond (notation of Schechter and Berger[7]) of the HIV PR p17/p24 substrate sequence was replaced with Pheψ[$PO_2^-CH_2N^+$]Pro. An expedient synthesis of the pseudoheptapeptide is outlined in Scheme I. The compound was obtained as separated *R* and *S* isomers (**7R** and **7S**) at the P_1 benzylic position.[8]

The inhibition of synthetic HIV PR[9] was measured using Lys-Ala-Arg-Val-Nle-pNO_2Phe-Glu-Ala-Nle-NH_2[10] adapted to an isocratic HPLC assay (K_m = 434 ± 25 μM, k_{cat} = 10 ± 0.2 s^{-1}; Table I). It was apparent that **7R** was potent in the nanomolar concentration range. Upon closer examination, the inhibition was observed to be time-dependent. The initiation of reactions with either enzyme or substrate gave burst and lag transients, respectively. In light of (1) the chemical nature of the ψ[$PO_2^-CH_2N^+$] functionality, (2) the establishment of equilibrium after enzyme–inhibitor preincubation, and (3) the equivalence of steady-state rates attained in burst and lag experiments, it is likely that the inhibitor binds in a reversible, noncovalent fashion. Hence, **7R** was studied as a slow-binding inhibitor.[11]

Table I. Kinetic Parameters for HIV PR Inhibitors[a]

parameter	7R[b]	7S[c]
K_i^* (nM)	8.2 ± 0.4	(54 ± 3) × 10^3
K_i (nM)	82 ± 8	(585 ± 60) × 10^3
k_5 (min^{-1})	0.15 ± 0.025	0.26 ± 0.045
k_6 (min^{-1})	0.017 ± 0.0020	0.026 ± 0.0031
k_5/k_6	9 ± 1	10 ± 1
$t_{1/2}$ (EI*) (min)	40 ± 5	26 ± 3

[a] Determined at 23 °C in 100 mM MES, 1 mM EDTA, 1 mM DTT, 200 mM NaCl, 0.1% Triton X-100 (pH 6.2), 1 nM enzyme, and 1500 μM substrate. [b] Weighted averages from stepwise analysis of five progress curves (K_i^* also evaluated from a complete double reciprocal experiment). [c] Weighted averages from stepwise analysis of three progress curves.

The final steady-state levels of inhibition revealed competitive inhibition. Since the values derived from an analysis of burst–transient progress curves satisfied required criteria, the mechanism of inhibition is in accord with the model illustrated in Scheme II.[12] The data are shown in Table I. The K_i^* value of 8 nM for **7R** ranks it highly as an HIV PR inhibitor and results in an inhibited enzyme of relatively long lifetime. Interestingly, K_i^* doubled at pH 4.7 in contrast to the pH profile of simple phosphinates.[13] The **7S** isomer, which binds >6 × 10^3-fold less tightly, also demonstrates slow-binding behavior. This is somewhat surprising given that the slow-binding phenomenon generally shows a strong stereochemical preference.[14] It is premature to speculate concerning protonation effects or conformations enforced by ψ[$PO_2^-CH_2N^+$] and adopted at the HIV PR active site.

Observations suggest the driving force for the time-dependent inhibition is localized in the Pheψ[$PO_2^-CH_2N^+$]Pro subunit. Remarkably, the dipeptide analogue **8R** is a competitive inhibitor (K_i^* = 270 μM) which does not equilibrate rapidly with the enzyme. While the peptide periphery provides specific interactions which ultimately lead to high affinity, it is not solely responsible for the changes occurring in the presteady state. The events which transpire in the slow equilibration to a tightened EI* complex are not clear, but ψ[$PO_2^-CH_2N^+$] seems a powerful design for a transition state, reaction intermediate, or tetrahedral collected product.[15]

Further kinetic characterization, development of potential pharmacologically useful HIV PR inhibitors, and application of

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$\psi[PO_2^-CH_2N^+]$ to other proteolytic enzymes are under investigation.

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Supplementary Material Available: Listing of synthetic procedures and experimental data relevant to the preparation of compound **7** (7 pages). Ordering information is given on any current masthead page.

Iso-Specific Ziegler–Natta Polymerization of α-Olefins with a Single-Component Organoyttrium Catalyst

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Three types of well-defined, homogeneous Ziegler–Natta α-olefin polymerization systems have been described recently: (1) two-component catalysts consisting of group 4 metallocene dihalides and a large excess of methylalumoxane cocatalyst;[1,2] (2) simpler two-component systems based on group 4 metallocene dialkyls with a stoichiometric (or near stoichiometric) amount of an activator such as $[C_6H_5(CH_3)_2NH^+][B(C_6F_5)_4^-]$,[3] $[(C_6H_5)_3C^+][B(C_6F_5)_4^-]$,[4] or $B(C_6F_5)_3$;[5] and (3) single-component catalysts such as Lewis base adducts of cationic group 4 metallocene alkyls[6] or the isoelectronic neutral group 3 or lanthanide metallocene hydrides or alkyls.[7] The group 4 metallocene/methylalumoxane and $[Cp_2MCH_3^+][B(R)(C_6F_5)_3^-]$ catalysts (M = Zr, Hf; R = C_6F_5, CH_3) exhibit higher activity in α-olefin polymerizations, and with the chiral, C_2-symmetric *ansa*-metallocene dihalide or dimethyl precursors (M = Ti, Zr, Hf) developed by Brintzinger, Ewen, Collins, and others, highly isotactic polypropylene is obtained.[1a-g,8] Unfortunately, the meso (C_s symmetric) isomer is normally formed along with the preferred chiral isomer in the synthesis of the metallocene dihalide.[8,9] Since the meso isomers generally produce atactic polypropylene and exhibit lower activity, a tedious separation of the meso isomer from the racemic isomer is normally required.

Herein we report the synthesis of the first iso-specific, single-component Ziegler–Natta polymerization catalyst, [*rac*-Me_2Si-(2-$SiMe_3$-4-$CMe_3C_5H_2)_2$YR]. Its simplicity makes it particularly

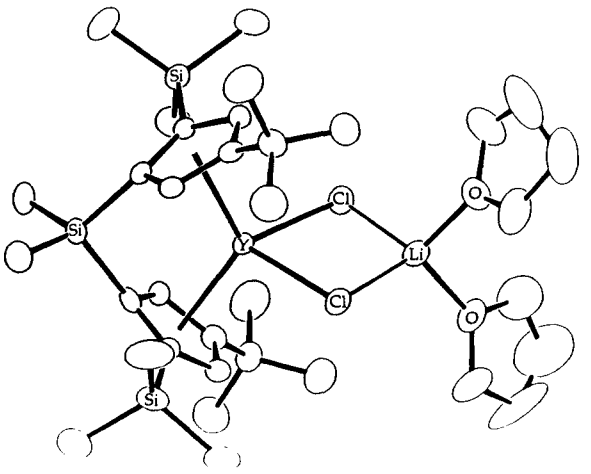

Figure 1. Molecular drawing of *rac*-$Me_2Si(2\text{-}SiMe_3\text{-}4\text{-}CMe_3C_5H_2)_2Y(\mu\text{-}Cl)_2Li(THF)_2$. All unlabeled atoms are carbon.

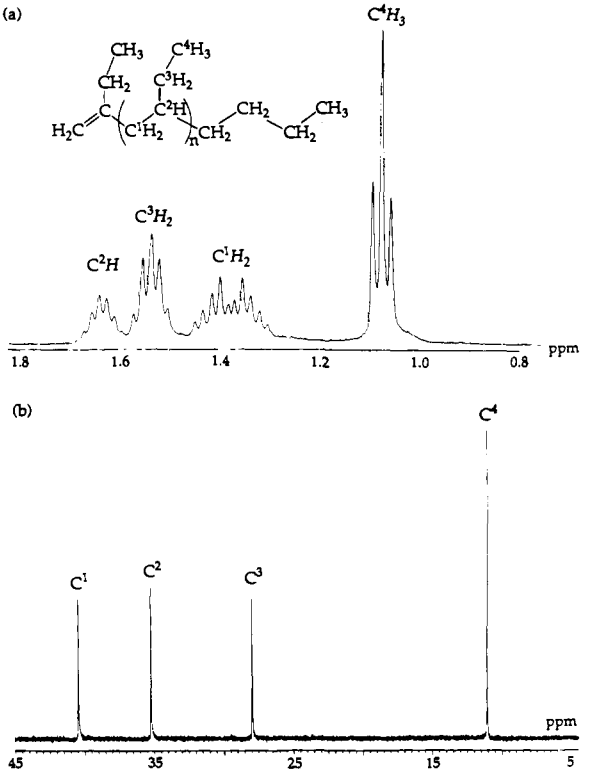

Figure 2. (a) ^1H NMR spectrum (400 MHz) (*o*-dichlorobenzene/benzene-d_6, 9:1 v:v, 100 °C) with tentative assignment of resonances. (b) ^{13}C NMR spectrum (100 MHz) (*o*-dichlorobenzene/benzene-d_6, 9:1 v:v, 100 °C) of poly(1-butene) obtained by polymerization of neat 1-butene at 25 °C with [*rac*-BpYH]$_2$.

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