No product of the acylation of the pyrrole nitrogen could be found.[10] However, the yield of CC-1065 by this route was only 5%.[11]

We then reexamined the earlier route, which had carried out the coupling on the amine **4b** (Scheme II), but had encountered difficulties in removing the benzyl protecting group.[4]

Condensation of **4b** with a carboxylic acid gives the amides in 70–80% yield. Reaction with mesyl chloride quantitatively yields the mesylates **5**. These compounds, however, are unstable and cannot be chromatographed without decomposition. Further, they often cyclize during attempted hydrogenolysis of the benzyl ether, leading to products of hydrogenolysis of the spirocyclopropyl ring system. In situ generated TMSI[4a] is highly unpredictable and often gives very poor yields of the desired product **6** or **3** (as is the case of CC-1065). Extensive efforts to find suitable substitute protecting groups for the benzyl moiety failed. We then tried changing the leaving group. Reaction of **5** with LiCl in DMF gives excellent yields of the chlorides **7** (70–90%). These compounds are significantly more stable and soluble than the mesylates and can readily be chromatographed. Phase transfer catalytic hydrogenolysis of **7** produces **8** in essentially quantitative yield. Interestingly, unlike **6**, the phenol chloride **8** does not close to **3** simply by treatment with 1–2 equiv of triethylamine in anhydrous solvents. In fact treatment of **8** with strong bases (LDA, NaH, KH, or KO-*t*-Bu) in a variety of solvents leads to **3** in only poor yield. The spirocyclopropyl derivative **3** can be produced, however, in essentially quantitative yield by reacting **8** (10 mg/mL) with a 1:1:1 mixture of triethylamine/acetonitrile/water at 25 °C. Thus, the closure appears to require, in addition to the push of the anion, also the pull of the hydration of the chloride by water in order to proceed. In this manner the CC-1065 analogues **3d** and **3e** were prepared from **4a** in an overall yield of 46% each.[4a,9]

While this multistep sequence has been greatly improved, it is still not a feasible route to CC-1065 or other complex analogues. It is, however, an efficient route to the Boc derivative **8f** (54% from **4a**), which is stable, highly soluble, and readily purified.

Happily, treatment of **8f** (8 mg/mL) with HCl gas in ethyl acetate (half to fully saturated at 25 °C) readily gives **9** (Scheme II). The free amine corresponding to **9** and the hydrochloride itself are extremely unstable, and short exposure to air turns them black. However, under an inert atmosphere it is possible to convert **9** to **8** by coupling with a carboxylic acid and EDC in overall yields of 70–90%. Cyclization in aqueous triethylamine affords **3**. With use of this chemistry the analogues **3a**,**b**,**d**,**e** were prepared.[9] Similarly natural CC-1065 and its enantiomer[12] were made on a 10–20-mg scale. The yields in this case are only 40–50% due to the greater complexity and insolubility in comparison with simpler analogues. The natural CC-1065 produced by this route is identical in all respects with CC-1065 isolated from natural sources.[1a,b,13] When taken with the total synthesis of PDE-1 dimer[2a,f,14] this constitutes a total synthesis of this important natural product. The ent-CC-1065 is also an extremely interesting material. Earlier reports[4a] of compounds in the ent series have disclosed them to be essentially inactive in the biological systems. Ent-CC-1065 on the other hand possesses both cytotoxicity[13] and biological effectiveness in its own right at similar concentrations to CC-1065 itself in the treatment of P388 leukemia in mice.[15] Further discussion in this area will be the subject to a separate communication.

Registry No. 3a, 110314-40-4; **3b**, 110352-06-2; **3d**, 101222-80-4; **3e**, 110314-48-2; (*S*)-**4a**, 101222-79-1; (*R*)-**4a**, 108867-95-4; **5d**, 108833-15-4; **5e**, 110314-43-7; **5f**, 110314-49-3; **7d**, 110314-44-8; **7e**, 110314-45-9; **7f**, 110314-50-6; **8a** (R = C_5H_{11}), 110314-52-8; **8b** (R = 1*H*-indol-2-yl), 110314-53-9; **8d**, 110314-46-0; **8e**, 110314-47-1; **8f**, 110314-51-7; **9**, 110314-54-0; CC-1065, 69866-21-3; ent-CC-1065, 110352-07-3; CPI, 110352-05-1; PE-I dimer, 98296-23-2; PDE-I dimer acid chloride, 110314-41-5; $CH_3(CH_2)_4CO_2H$, 142-62-1; *t*-$BuOCO_2H$, 51300-90-4; hexanoyl chloride, 142-61-0; 1*H*-indole-2-carbonyl chloride, 58881-45-1; 5-[[(1*H*-indol-2-yl)carbonyl]amino]-1*H*-indole-2-carboxylic acid, 101134-91-2; 5-[[(benzofuran-2-yl)carbonyl]amino]-1*H*-indole-2-carboxylic acid, 110314-42-6; 1*H*-indole-2-carboxylic acid, 1477-50-5.

(9) NMR and mass spectral data are presented. Compound **3a**: NMR ($CDCl_3$) δ 0.9 (3 H, t, J = 7 Hz), 1.15–1.45 (6 H, m), 1.6–1.8 (1 H, m), 2.0 (4 H, s + m), 2.5 (2 H, t, J = 7 Hz), 2.75–3.0 (1 H, m), 3.9–4.25 (2 H, m), 6.7 (1 H, m), 6.9 (1 H, m), 10.35 (1 H, brs); MS (FAB), calcd for $C_{18}H_{23}N_2O_2$ 299.1759, found 299.1745. Compound **3b**: NMR (DMSO-d_6) δ 1.38 (1 H, t, J = 4 Hz), 2.0 (4 H, brs), 3.2 (1 H, m), 4.45 (2 H, m), 6.72 (1 H, s), 6.95 (1 H, m), 7.15–7.8 (5 H, m), 11.55 (1 H, brs); MS, m/e 343 (M^+), 326, 200, 199, 144. Compound **3d**: see ref 4a. Compound **3e**: NMR (DMF-d_7) δ 1.51 (1 H, t, J = 5 Hz, 2.04–210 (1 H, m), 2.102 (3 H, s), 3.24–3.31 (1 H, m), 4.60 (1 H, d, J = 10 Hz), 4.69 (1 H, dd, J = 4, 10 Hz), 6.84 (1 H, s), 7.03 (1 H, s), 7.32 (1 H, s), 7.39–7.92 (7 H, m), 8.46 (1 H, d, J = 2 Hz), 10.6 (1 H, s), 11.83 (1 H, s); MS (FAB), calcd for $C_{30}H_{23}N_4O_4$ 503.1719, found 503.1742. Compound **5f**: NMR ($CDCl_3$) δ 1.6 (9 H, s), 2.3 (3 H, s), 3.4–4.4 (6 H, m), 5.15 (2 H, s), 6.9 (1 H, s), 7.2–7.8 (6 H, m), 8.5 (1 H, s); MS (FAB), calcd for $C_{24}H_{28}N_2O_4$ 408.2049, found 408.2051. Compound **7f**: NMR ($CDCl_3$) δ 1.6 (9 H, s), 2.4 (3 H, s), 3.2–4.5 (5 H, m), 5.2 (2 H, s), 7.0 (1 H, s), 7.3–7.7 (6 H, m), 8.3 (1 H, m); MS (FAB), calcd for $C_{24}H_{27}ClN_2O_3$ 426.1710, found 426.1721. Compound **8f**: NMR ($CDCl_3$, acetone-d_6) δ 1.6 (9 H, s), 2.4 (3 H, s), 3.3–4.4 (5 H, m), 7.1 (1 H, s), 7.4 (1 H, s), 8.9 (1 H, s), 9.7 (1 H, s); MS (FAB), calcd for $C_{17}H_{21}ClN_2O_3$ 336.1241, found 336.1230.

(10) The structure of the desired product could easily be shown by comparison with authentic material prepared by the Warpehoski chemistry[4] and by 500 MHz COSY experiments which showed the pyrrole N–H coupled to the 2-pyrrole hydrogen and that to the pyrrole methyl group. We thank T. A. Scahill and R. M. Jensen of the Physical and Analytical Chemistry Unit of the Upjohn Company for running these NMR spectra.

(11) The reaction was run on a 1–2-mg scale. The material was shown to be identical with CC-1065 by TLC and bioassay.

(12) Prepared from the enantiomer of compound **4**.[4a]

(13) The NMR and UV of natural, synthetic, and ent-CC-1065 are identical within experimental error (see ref 1b). The $[\alpha]_D^{25}$ for natural CC-1065, synthetic CC-1065, and ent-CC-1065 are, respectively, +97°, +98°, and −96° (c 0.2, DMF). The in vitro L 1210 is given as the concentration which inhibits the growth of logarithmically growing murine leukemia L 1210 cells by 50% [ID_{50}]: natural CC-1065, $ID_{50} = 1.9 \times 10^{-12}$ g/mL; synthetic $ID_{50} = 2.5 \times 10^{-12}$ g/mL; ent, $ID_{50} = 4.5 \times 10^{-12}$ g/mL. We thank the Upjohn scientists L. H. Li and J. W. Culp for the in vitro L 1210 data.

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(15) Private communication from L. H. Li and T. F. DeKoning of the Upjohn Cancer and Viral Diseases Unit. We thank these authors for release of this information prior to publication.

1,3-Hydrogen Shifts in Olefin Radical Cations: An ab Initio Study

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Recent work on cycloadditions[1] involving radical cations has demonstrated that molecular ions can undergo extremely facile reactions that would be Woodward–Hoffmann forbidden for the neutral molecule. Another class of reactions treated by Woodward and Hoffmann,[2] sigmatropic rearrangements, also behave differently in radical cations and neutral radicals than in closed shell molecules[3] but have not been investigated in detail, especially in the case of hydrogen shifts. Recently, however, Fujisawa et al.[4] reported that the reaction of the ethylene radical cation with ethylene in a Freon matrix leads to a radical cation that has

(1) See: Lorenz, K. T.; Bauld, N. L. *J. Am. Chem. Soc.* **1987**, *109*, 1157 and references therein.

(2) See: Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry*; Academic Press: New York, 1970.

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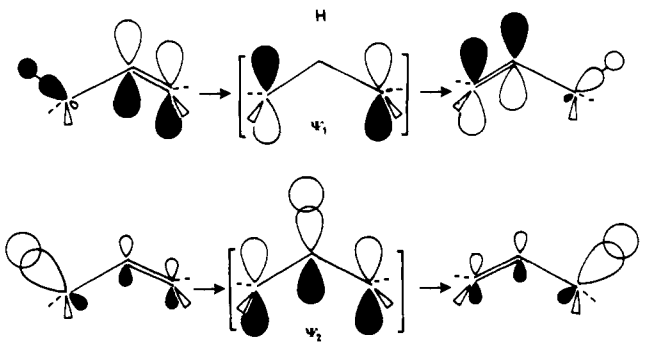
Table I. Total (au) and Relative (kcal mol^{-1}) Energies for **1–4** and Their Isomers

		UF/6-31G*		UMP2/6-31G*	
species	NIMAG[a]	tot. energy	rel energy	tot. energy	rel energy
1, C_s	0	−116.77358	0.0	−117.11220	0.0
2, C_s	1	−116.73798	22.3	−117.07279	24.7
3, C_s	1	−116.71410	37.3	−117.06508	29.6[c]
4, $C_2 \rightarrow C_{2v}$[b]	2	−116.69784	47.5	−117.05190	37.7
$C_3H_5^+ + H^\bullet$		−116.69144	51.5	−117.04125	44.5[d]
$C_3H_5^\bullet + H^+$		−116.46810	191.7	−116.80964	189.9[e]

[a] The numbers of imaginary frequencies obtained on diagonalization of the force constant matrix at UHF-6-31G*. [b] The optimization was constrained to C_2 symmetry, but a C_{2v} structure resulted. [c] McLafferty et al.[19] give an activation energy for this process of about 34 kcal mol^{-1} in a figure. This estimate is based on deuterium scrambling in propene$^{+\bullet}$ and on the cyclopropane$^{+\bullet}$ to propene$^{+\bullet}$ rearrangement. [d] The experimental value[18] is 47.8 kcal mol^{-1}. [e] The experimental value[18] is 175.4 kcal mol^{-1}.

tentatively been identified as 1-butene$^{\bullet+}$. Futhermore, this radical cation rearranges at higher temperatures to give the 2-butene radical cation. Assuming that the initial reaction produces a radical cation of the type $(CH_2)_4^{\bullet+}$,[5] two formal 1,3-hydrogen shifts are required to reach 2-butene$^{\bullet+}$. Similarly, Courtneidge and Davies[6] have observed the rearrangement of the di-*tert*-butylacetylene radical cation to the hexamethylbutadiene radical cation. Although the authors proposed consecutive 1,2-methyl shifts to account for their observations, two 1,3-shifts seem more attractive because the intermediate would then be an allene radical cation, rather than a carbene radical cation. There are other indications that radical on sigmatropic rearrangements may often be very facile. Dinnocenzo[7] has recently observed 1,3-sigmatropic ring expansions in vinyl cyclopropane radical cations, and Roth[8] has pointed out the "nonvertical" nature of 1,5-hexadiene radical cations, which suggests that, for instance, the Cope rearrangement should be very easy in radical cation systems.

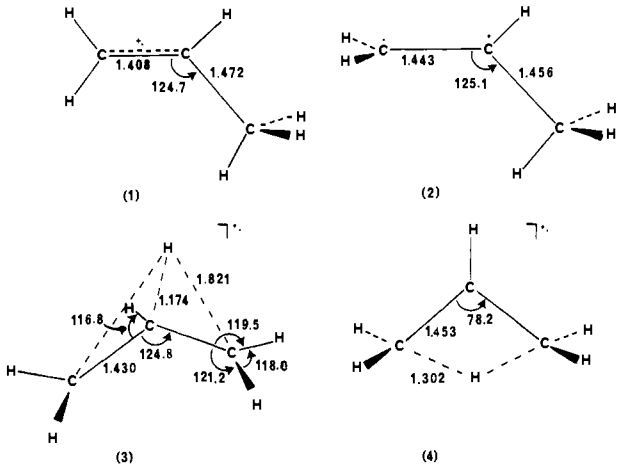
The orbital process involved in a superfacial 1,3-hydrogen shift is shown below. The unfavorable nonbonding ψ_1 generally de-



stabilizes the transition state, so that this reaction can be considered forbidden. However, if the π-stabilization energy gained in ψ_2 on going to the transition state is comparable to the dissociation energy of the migrating σ-bond, a suprafacial 1,3-shift may become energetically feasible. This is illustrated by allyl magnesium hydride and allyllithium.[9] The former has a low barrier to a 1,3-MgH shift, and the latter has a C_s bridged structure.

The propene radical cation is another such case. The migrating σ-bond is weakened by hyperconjugation in the minimum energy structure, and there is considerable energy to be gained in allyl delocalization on going to the suprafacial 1,3-shift transition state. This communication therefore reports the results of ab initio molecular orbital calculations[10] on the 1,3-hydrogen shift process in propene$^{\bullet+}$.

The equilibrium structure of propene$^{\bullet+}$ (**1**) is found to have a planar C=C linkage at UHF/6-31G*. Experimental results have



been interpreted as indicating a twisted structure,[11] but it has recently been shown that the observed ESR splittings are consistent with a planar double bond.[12] The transition state for rotation about the C=C bond in **2** was found to be 24.7 kcal mol^{-1} less stable than in **1**. This barrier is about that expected for half a CC double bond when the extra hyperconjugation in the transition state is taken into account. The activation energy for a superfacial 1,3-shift in **3** was found to be only 29.6 kcal mol^{-1}, as shown in Table I. Diagonalization of the force constant matrix showed that, in contrast to neutral propene,[13] this structure is indeed the transition state for the hydrogen migration and not for a methylene group disrotation. Structure **4**, a model for a possible antarafacial 1,3-hydrogen shift transition state, is found to be 8 kcal mol^{-1} less favorable than **3**, and diagonalization of the force constant matrix shows it to have two imaginary frequencies, so that **3** is the only transition state located for the 1,3-hydrogen shift. Table I also shows the energies for the products of the two possible modes of dissociation of $C_3H_6^{\bullet+}$ into the allyl cation and a hydrogen atom or into the allyl radical plus a proton. The 1,3-shift transition state **3** is bound by 14.9 kcal mol^{-1} relative to the loss of a hydrogen atom, so that the sigmatropic shift is a concerted reaction with a transition state well below the dissociation limit.

These results contrast strongly with those obtained by Schlegel et al.[13] for the corresponding reaction in neutral propene and illustrate once more the major changes in behavior which can occur on loss of an electron. One curious feature of the transition state **3** is its resemblance to an edge–edge trimethylene radical cation. The allyl moiety is essentially planar (the central CH bond lies 13.2° below the CCC plane, and the inner and outer terminal CH bonds are 9.4° below and 2.3° above it, respectively) with a CCC angle of 124.8°. The distance between the central carbon and the migrating hydrogen is only 1.174 Å. The hydrogen out-of-plane deformations are reminiscent of allyllithium.[9] A face–edge trimethylene radical cation has been proposed as the species formed by ring opening of the cyclopropane radical cation in a Freon 113

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Matrix,[14] but calculations at the UHF/6-31G* level do not reveal a stable gas-phase structure for this species. The short C_2–H distance in **3** suggests that the 1,3-shift should be better seen as two consecutive 1,2-shifts. Although 1,2-hydrogen shifts barriers are close to the dissociation limit in most radical systems,[15-17] the involvement of the double bond in this case facilitates the migration.

The above results not only suggest that suprafacial 1,3-hydrogen shifts in olefin radical cations should be facile processes but also hint at a general willingness of radical cations to undergo sigmatropic rearrangements that would be difficult in the neutral parent molecules.

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Registry No. 1, 34504-10-4.

Supplementary Material Available: Archive entries for MP2/6-31G*//6-31G* calculations on **1–4** (2 pages). Ordering information is given on any current masthead page.

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Metalloregulation in the Sequence Specific Binding of Synthetic Molecules to DNA

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Specific metal cations exert remarkable effects on the transcription of several prokaryotic and eukaryotic genes.[1] Recently, the DNA-binding eukaryotic transcription factor TFIIIA has been characterized as a series of peptide fingers connected by zinc-binding domains.[1a] These observations raise the issue of whether the binding of synthetic molecules to DNA could in some way be regulated by the addition of specific metal ions.[2]

Bis(netropsin)-3,6,9,12,15-pentaoxaheptadecanediamide (Figure 1)[3] was synthesized to test the possibility of *metalloregulation* in the sequence specific binding of a small molecule to DNA. **1** is a dimer of netropsin analogues[4] connected by a tetraethylene glycol tether, a multidentate acyclic neutral ligand (podand) for metal cations. The tether's terminal glycolamide groups provide additional oxygen donors and might allow **1** to wrap up as a pseudomacrocycle which would mimic the hole size of 18-crown-6.[5] For simultaneous binding of the dipeptide subunits,[6] one might anticipate that the energetic benefit of filling the pseudomacrocycle with a specific metal cation would be important. Attachment of EDTA to one terminus of the molecule allows use of the affinity cleaving method[7] to determine the DNA-binding efficiency, sequence specificity, and binding site size of **1**·Fe(II), in the presence and absence of various alkali, alkaline earth and transition-metal cations.[8,9]

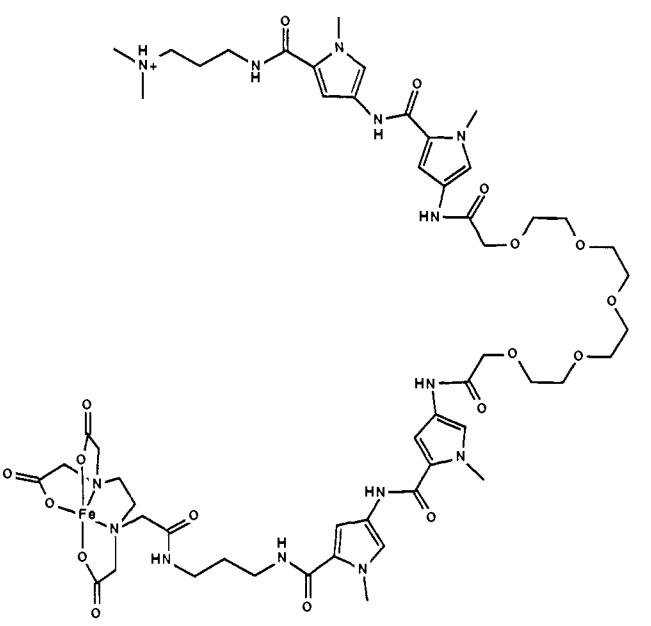

Figure 1. Bis(netropsin)-3,6,9,12,15-pentaoxaheptadecanediamide-EDTA·Fe (**1**·Fe).

A 517 base pair restriction fragment (Eco RI/Rsa I) from plasmid pBR322 DNA, labeled with ^{32}P on the 5′ end, was incubated with **1**·Fe(II) (20 μM) in the presence of various cations (1 mM)[8] for 2 h at 37 °C (pH 7.6). Dithiothreitol (1 mM) was added to initiate the cleavage reactions which were allowed to proceed for 1.5 h at 37 °C. The DNA cleavage products were separated on a DNA sequencing gel and visualized by autoradiography (Figure 2). **1**·Fe(II) (20 μM) in the absence of metal cation or in the presence of 1 mM concentrations of Na^+, K^+, Mg^{2+}, Ca^{2+}, NH_4^+, Ag^+, Ni^{2+}, Cd^{2+}, or Hg^{2+} produces little DNA cleavage.[8,9] However, addition of Sr^{2+} or Ba^{2+} results in strong

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