showed that the intensity of the upfield resonance increased as the downfield resonance disappeared; the eventual result was the spectrum of the equilibrated protein. The upfield resonance was not observed in spectra of PMS-MSMC taken immediately after dissolution, even at the minimum number of scans required to detect the ^{13}C-enriched *S*-methyl group (~2500 scans).

The changing spectrum of nonequilibrated MSMC solutions does not result from autolysis or denaturation of protein. During a typical NMR experiment, none of the original activity of the modified enzyme toward PNPP is lost in 9 h, and only 15% is lost in 14 h. A more attractive explanation for the ^{13}C NMR results is that in lyophilized MSMC the cationic side chain of the SMM-192 residue is tucked into the active site where it forms a salt with the anionic side chain of a nearby amino acid residue, but upon exposure of the modified enzyme to a solution containing competing counterions, it rotates into solution. The identity of the anionic group is uncertain, but Asp-194, a nearby residue involved in a buried salt bridge with Ile-16,[14] is a likely candidate. The greater half-bandwidth of the transient downfield resonance compared with that of the upfield resonance ($W_H \sim 3.5$ Hz vs. $W_H \sim 1.9$ Hz) supports this proposal, since it suggests a greater rotational constraint on the SMM residue in the nonequilibrated fraction of protein than in the equilibrated fraction.[15] The ^{13}C NMR spectra obtained immediately after dissolution of PMS-MSMC also support this view; evidently the interaction in lyophilized MSMC giving rise to the downfield resonance is blocked by the presence of the bulky PMS group at the active site of the enzyme. Although we are uncertain of the reasons for the sluggishness of the transformation undergone by the SMM-192 residue as lyophilized MSMC solutions equilibrate, a study of [*S*-phenacylmethionine-192]-α-chymotrypsin provides a precedent. At pH 7 the *S*-phenacyl group of this protein is irreversibly locked in a buried environment.[16] If, as proposed, lyophilization provokes movement of the SMM-192 side chain of MSMC from solution to a constrained environment within the active site, reduced steric or other requirements of *S*-methyl compared with *S*-phenacyl may allow the reverse process to occur, albeit slowly, upon dissolution of the protein at pH 7.

Acknowledgment. This work was supported by National Institutes of Health Grant GM 18652.

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Tetracoordinate Planar Carbon: A Singlet Biradical

Sir:

Coincident with the centenary of the van't Hoff and LeBel proposal that tetracoordinate carbon prefers a tetrahedral shape, the last 10 years has witnessed a persistent interest in the prospect of either foiling or exploiting nature in order to generate the planar tetracoordinate species.[1-9] Numerous theoretical studies have yielded estimates of 95-250 kcal/mol for the energy requirement to flatten CH_4.[3a,4-6] Simultaneously, a series of strategies have been recommended as a guide to the experimentalist in his search for the elusive planar structure **1**. These have drawn their inspiration from two main sources. The first pays tribute to the organic chemist's synthetic ingenuity and requires the CR_4 subunit to be nested in a larger frame designed to enforce the desired geometric distortion, for example, *trans*-fenestrane **2**.[1b,5c8,9]

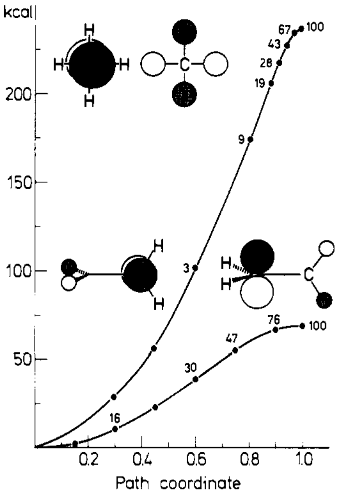
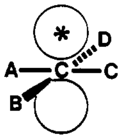


Figure 1. The PRDDO-GVB linear synchronous transit (LST) pathways connect planar ethylene and tetrahedral methane [path coordinate (pc) = 0.0] to perpendicular D_{2d} ethylene and planar D_{4h} methane (pc = 1.0), respectively. The percentage of biradical character along the isomerization pathways is indicated at points along each curve and corresponds to the degree of occupation of the least populated GVB natural orbital. The GVB split-pair orbitals, linear combinations of the singly occupied natural orbitals, are depicted for the $CH_2{=}CH_2$ and CH_4 biradicals (pc = 1.0).[17]



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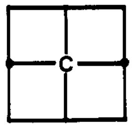

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The second and more rigorous approach is a consequence of single-determinant molecular orbital theory's prediction that the lowest singlet state of planar tetracoordinate carbon possesses a

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(2) (a) F. T. Smith, *J. Chem. Phys.*, **29**, 235 (1958); R. Hoffmann, *J. Am. Chem. Soc.*, **90**, 1475 (1968); H. Kollmar, *ibid.*, **95**, 966 (1973); (b) K. E. Gilbert and J. E. Baldwin, *ibid.*, **98**, 1593 (1976).

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Table I. PRDDO and MNDO Energy Differences between Ground-State Tetrahedral Methane (T_d, $^1A_1$) and Various States of Planar (D_{4h}) and Pyramidal (C_{4v}) Isomers Charge Distributions and C-H Distances for D_{4h} and C_{4v} Methane

	$\Delta E(T_d - D_{4h}/C_{4v})$,[a] kcal/mol		APS charge densities,[b] q_C/q_H		optimized rC–H distances, Å	
electronic state	MNDO	PRDDO	MNDO	PRDDO	MNDO	PRDDO
D_{4h}, 1 (A–D = H)						
$^1A_{1g}$ (* = ··)	141	256[c]	−1.0/+0.26	−0.80/+0.20	1.110	1.075
$^1B_{2u}$ (* = ·)	116	243[d]	0.0/0.0	+0.26/−0.065	1.141	1.147
		228[e]		−0.052/+0.013		1.167
		225[f]		−0.056/+0.014		1.164
		213[g]		−0.056/+0.014		1.171
$^3B_{2u}$ (* = ·)	116[h]	225[e]	0.0/0.0	−0.056/+0.014	1.141	1.164
C_{4v}, 4						
$^1A_1$	[j]	233[c] (113)[i]		−0.52/+0.13		1.155
$^1B_1$	[j]	206[d] (111)[i]		−0.44/+0.11		1.185
		228[e] (177)[i]		−0.052/+0.013		1.167
		225[f] (173)[i]		−0.052/+0.013		1.164
		212[g] (177)[i]		−0.056/+0.014		1.173
$^3B_1$	[j]	225[e] (173)[i]		−0.044/+0.011		1.168

[a] Energy differences refer to tetrahedral CH_4 calculated at the MNDO (ref 10) or the PRDDO-SCF (ref 11a,b) level as the common energy zero. For the multideterminant PRDDO methods, see ref 11c. [b] D. R. Armstrong, R. G. Perkins, and J. J. P. Stewart, *J. Chem. Soc., Dalton Trans.*, 838 (1973). [c] PRDDO-SCF. [d] PRDDO-CI; all single and diagonal double excitations from the filled orbitals 2–5 to tne virtual orbitals 6–9 were included. [e] PRDDO-RHF. [f] PRDDO-GVB. [g] PRDDO-GVB-CI; all single and diagonal double excitations from the filled orbitals 2–5 to the virtual orbitals 6–9 were included. [h] Since MNDO (ref 10) neglects two-center exchange integrals, the MNDO singlet-triplet separation for CH_4 is zero. [i] The nonadjacent HCH angle, deg. [j] The planar shape lies at the energy minimum.

Table II. PRDDO Energy Differences between Some Ground-State Tetrahedral Hydrocarbons and Their Planar Isomers[a,b]

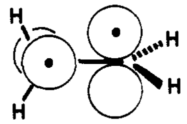
	CH_4	5	6	7	8	9	10	11
S_0[d]	256 (240)[c]	193 (198)[c]	217 (225)[c]	174 (189)[c] 168[e]	133 125[e]	120 113[e]	105 (137)[c] 95[e]	68 58[e]
S_1[f]	228 225[e]	180 176[e]	200 163[e]	240	162	155	310	198
T_1[f]	225	178	163	237	161	151	240	151

[a] Except for CH_4, the geometries of all tetrahedral and planar species were generated by a complete MINDO/3 optimization. The planar forms were reoptimized as MINDO/3 triplets. The resulting structures were then subjected to single-point calculations at the PRDDO level indicated, S_0 employing the closed-shell geometries, S_1 and T_1 the MINDO/3 triplet shapes. [b] The energy zero in each case is the PRDDO-SCF single-determinant tetrahedral structure. A variety of energetically similar excited states have been considered for each case. S_0, S_1, and T_1 refer to the lowest energy closed- and open-shell singlet and triplet states, respectively, obtained in the present study. [c] STO-3G energy differences employing standard geometries; ref 4a. [d] PRDDO-SCF; ref 11a,b. [e] PRDDO-GVB; ref 11c. [f] PRDDO-RHF; ref 11c.

lone electron pair in a p-type orbital on the carbon in question (**1**, * = ··).[1,3-7] Substitution patterns which remove p electrons from this center have thereby emerged as candidates for either low-lying stereomutation or inversion transition states[2] or observable entities resting in potential energy minima.[1c,3] Simultaneous π-acceptor and σ-donor substituents have recently appeared particularly attractive.[4a,7]

We point out that the lowest singlet state of planarized methane (D_{4h}) may be an open-shell singlet of $^1B_{2u}$ symmetry, one electron residing in the carbon p orbital (**1**, * = ·, a_{2u}), the other found in the antisymmetric hydrogen d-type MO (b_{1g}) shown in Figure 1. MNDO[10] and PRDDO–GVB[11] calculations suggest the planar biradical singlet to be 25–30 kcal/mol below the closed-shell $^1A_1$ state. A similar description is obtained either by adding a simple HOMO–LUMO configuration interaction to the MNDO or PRDDO single-determinant wave function [$\Delta\Delta E$(CI − closed shell) = 25 and 13 kcal/mol, respectively] or by carrying out a fuller PRDDO–GVB-CI[11c] calculation ($\Delta\Delta E$ = 43 kcal/mol). In all cases, the b_{1g} MO carries a single electron as expected for genuine biradical character.

Larger basis sets and more extensive CI can be expected to refine quantitative aspects of the bonding picture.[12] However, qualitatively, the situation is completely analogous to the process of rotation about the C=C bond of ethylene, whereby transit to the perpendicular D_{2d} transition state closes the HOMO–LUMO energy gap and gradually yields the relatively low-energy $^1B_1$ diradical symbolized by **3**.[13] Planarization of methane has been followed by constructing an LST pathway between the limiting molecular shapes at the PRDDO–GVB level.[11b,c] The closed-shell tetrahedral ground state is transformed smoothly and continuously uphill in energy through a biradicaloid region in which uncoupling of the HOMO electron pair begins. The transformation terminates at the planar $^1B_1$ biradical (Figure 1). Significantly, within the GVB framework, biradical character emerges only during the final 15–20% of the pathway to the planar structure and corresponds to an H–C–H angle deformation from 165 to 180°. This is to be contrasted with ethylene which develops biradical attributes over 70–75% of the path to the twisted D_{2d} species (Figure 1).



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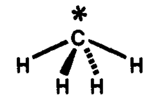

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Further optimization by PRDDO reveals a slight preference for the square-pyramidal C_{4v} geometry **4**, but the energy minima

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(10) M. J. S. Dewar and W. Thiel, *J. Am. Chem. Soc.*, **99**, 4899 (1977); W. Thiel, QCPE, **10**, 353 (1978).

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are found to be quite shallow (cf. Table I). Clearly, previous single-determinant calculations on planar singlet CR_4 have produced the lower of the two zwitterionic states.[3-6] The charge distributions given in Table I are indicative.

It is necessary to note that triplet planar methane derivatives were calculated as early as 1972 to be either the most stable electronic state or energetically competitive with the closed-shell singlet **1** (* = ··).[6] Our calculations yield a similar result (Table I). The importance of a biradical constitution for flattened carbon structures has been alluded to by the observation that electron correlation preferentially stabilizes $^1A_1$ singlets.[4,7] In spite of these reports, the closed-shell singlet embellished by a lone electron pair has been the standard for comparison and the electronic entity consistently described as the experimental goal.[1b,2b,3b,4,5c,7-9]

The biradical description for planar or near-planar CH_4 is not limited to the parent. Cyclopropane, suggested as a candidate for stereomutation via the planar transition state **5**,[2a] and cyclopropene likewise prefer open-shell singlet states by ΔE(open − closed) = 17.3 and 53.3 kcal/mol, respectively (Table II). It should be noted that open-shell singlet and triplet energies are comparable. On the other hand, the five- and six-membered ring structures **7**–**11** are all predicted to exist as closed-shell molecules with a carbon lone electron pair as depicted by **1** (* = ··) (Table II). The relative ordering of singlet states for planar methane, **5**, and **6** on the one hand and cycles **7**–**11** on the other appears to arise from a combination of MO reorganization and electron repulsion effects. Specifically, the electron repulsion implied by the p-type orbital of **1** (* = ··), unless mediated by delocalization, is sufficient to uncouple the electron pair.[14]

5

6

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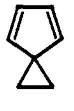

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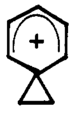

11

As has been noted previously, the incorporation of a planar carbon moiety in a three-membered ring or in a cyclic unit with $(4N + 2)\pi$ electrons lowers the planarization barrier relative to methane.[1c,3,4a] The effect persists regardless of the pairing scheme favored by PRDDO. However, in the practical design of synthetic routes to or through tetracoordinate planar carbon, the most expeditious substrates would appear to be those employing a delocalized π system and molecular charge. In this spirit, the planar D_{4h} ammonium ion, NH_4^+, lies 166 kcal/mol above the tetrahedral geometry, a gain of 90 kcal/mol relative to CH_4,[15] and is predicted by PRDDO–GVB to be a closed-shell ground state. All-carbon structures such as fenestrane **2** and the paddlanes,[1b,5c,8,9] on the contrary, are suggested to evidence closed-shell qualities only by deviating sufficiently from the sought-after planarity.

Acknowledgment. We are grateful to the Danish Natural Science Research Council for generous provision of computer funds (J.nr. 511-15446) and to the University of Copenhagen for a scholar stipendium to D.C. We are likewise indebted to Professor Thomas Halgren (City College of the City University of New York) for patient instruction in the manipulation of PRDDO and for an appreciation of its utility for describing biradicals. Provocative discussions with Professor Paul von R. Schleyer (Universität Erlangen-Nürnberg) and the pioneering work of his group provided the impetus for our work.

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[14] For example, the HOMO–LUMO gap for planar methane at the PRDDO–RHF level is larger than that for **5**, **6**, and **7**–**10**. Calculated values of two-electron repulsion integrals intimate that the dominating factor stabilizing the open-shell singlets is intraorbital Coulomb repulsion.

[15] The GAUSSIAN 70 program series yields $\Delta E_{NH_4^+}$(tetrahedral − planar) = 165 (STO-3G) and 129 kcal/mol (4-31G), corresponding to reduced barriers to flattening of 75 and 39 kcal/mol, respectively, relative to $^1A_1$ methane.[5b] More recent calculations at the 6-31G* and MP2/6-31G* levels lead to a similar reduction in planarization energies for the ammonium ion.[4b,16]

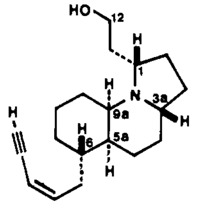
[16] We are grateful to Professor Schleyer for informing us of these results prior to publication.

[17] D. Döhnert and J. Koutecký, *J. Am. Chem. Soc.*, **102**, 1789 (1980).

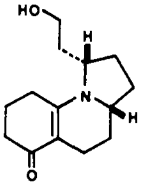
Total Synthesis of (±)-Gephyrotoxin

Sir:

Gephyrotoxin (**1**) is one of a variety of alkaloids isolated from the skin extracts of the Columbian frog, *Dendrobates histrionicus*. The structure of gephyrotoxin, including its absolute configuration, was elucidated by chemical[1,2] and X-ray[2] studies. Recent publication of a total synthesis of (±)-perhydrogephyrotoxin by Overman[3] and a model study for the ring construction of the alkaloid by Hart[4] prompted us to report the first, highly stereoselective total synthesis of (±)-gephyrotoxin. The unique aspect of this synthesis is that all five asymmetric centers were stereoselectively introduced through hydrogenation reactions. One of the key strategies of this synthesis involved the use of the hydroxyethyl side chain to direct the stereochemical course of the hydrogenation of the vinylogous amide **2**.



1, gephyrotoxin



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The synthesis of the vinylogous amide **2**[5a] (mp 153–154 °C; NMR ($CDCl_3$) δ 3.8–4.2 (2 H, m), 3.69 (2 H, t, J = 6.0 Hz); UV (MeOH) λ_{max} 319 nm (ϵ 30 900)) is summarized in Scheme I. Introduction of the first two asymmetric centers at C-1 and C-3a[6] was achieved by the hydrogenation of compound **4**, yielding a 12:1 ratio[7a] of the *cis*- and *trans*-pyrrolidines. The overall yield of **2** from **3** was about 20%.

Hydrogenation of the vinylogous amide **2** by using 10% palladium on charcoal in ethyl acetate under 60 psi hydrogen pressure at room temperature gave a single amino alcohol, **8**[5b] (51% yield; NMR ($CDCl_3$) δ 3.72 (2 H, dt, J = 3.0, 7.0 Hz)) along with the hydrogenolysis product **9**[5b] (19% yield). The stereochemistry of the amino alcohol **8** was determined by the X-ray analysis of its *p*-bromobenzenesulfonate salt[5a] (mp 160–162 °C).[8] The ste-

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[1] Tokuyama, T.; Uenoyama, K.; Brown, G.; Daly, J. W.; Witkop, B. *Helv. Chim. Acta* **1974**, *57*, 2597.

[2] Daly, J. W.; Witkop, B.; Tokuyama, T.; Nishikawa, T.; Karle, I. L. *Helv. Chim. Acta* **1977**, *60*, 1128.

[3] Overman, L. E.; Fukaya, C. *J. Am. Chem. Soc.* **1980**, *102*, 1454.

[4] Hart, D. J. *J. Am. Chem. Soc.* **1980**, *102*, 397.

[5] (a) Satisfactory elemental analysis and spectroscopic data (NMR, IR, UV, MS) have been obtained for this substance. (b) Satisfactory spectroscopic data (NMR, IR, UV, MS) have been obtained for this substance.

[6] Numbering in this paper corresponds to that of gephyrotoxin; see ref 2 and also structure **1** of this paper.

[7] This ratio was based on (a) the isolated yield of **5** and its stereoisomer; (b) the isolated yield of **10** and its stereoisomer and also of **11** and its stereoisomer; (c) the high-performance LC analysis. Base-line to base-line separation of the two diastereomers was observed for the compounds having X = CH_2CO_2Et, Y = COC_6H_5 in structures **15** and **16**.

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