Table I. Isotope Effect, k_H/k_D, for Reaction 1[a,b]

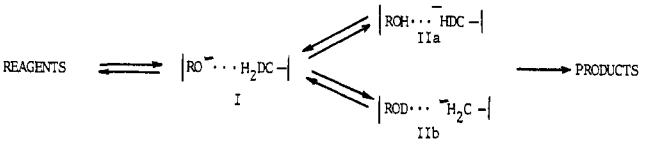
	CH_3O^-	$C_2H_5O^-$	$(CH_3)_2CHO^-$	$(CH_3)_3CCO^-$	$(CH_3)_3CCH_2O^-$
p-$CH_3C_6H_4CH_2D$	0.83 (1.7)[c]				
$C_6H_5CH_2D$	0.84 (−0.2)				
$C_6H_5CHDCH_3$	0.88 (−0.9)	0.81 (2.3)[c]			
m-$FC_6H_4CH_2D$	1.49 (−6.5)	0.97 (−3.5)	0.81 (−1.3)	0.66 (−0.5)	0.69 (1)
p-$ClC_6H_4CH_2D$	1.59 (−7)	1.31 (−4)	0.94 (−2)	0.77 (−1)	0.76 (0.3)
m-$ClC_6H_4CH_2D$	1.56 (−8.5)	1.28 (−5.5)	1.15 (−3.5)	0.71 (−2.5)	0.74 (−1)

[a] Typical root-mean-square deviation for the measurements is better than ±0.07. [b] The exothermicities ($\Delta H°$) of the reactions are given in parentheses in kcal mol^{-1}. The first three lines are accurate values based on the acidity scale of Bartmess, J. E.; McIver, R. T., Jr., private communication. The other values are estimates based on the assumption that the substituent effect in toluenes is similar to that observed in the gas-phase acidity of phenols. [c] These reactions were studied at neutral pressures above 10^{-5} Torr.

within the framework of transition-state (TS) theory in terms of the symmetry or extent of proton transfer in the TS.

Our measurements of k_H/k_D by ICR[7] are shown in Table I along with the thermochemistry for the reactions. The results show a definite trend for k_H/k_D starting as a normal isotope effect for appreciably exothermic reactions (>3 kcal mol^{-1}) and proceeding smoothly toward an inverse isotope effect as the reaction approaches thermoneutrality or becomes endothermic.

Our observations can be rationalized in terms of the likely potential energy surface for these reactions. Brauman[8] has recently proposed a dynamic model to account for the slowness of several reactions involving carbon acids in the gas phase. For our systems, the reaction can be represented as going through a double minima potential with a central energy barrier. The intermediate complexes (I and II) are expected to be weakly



bound species with stabilities in the range of 10 kcal mol^{-1}. For very exothermic processes, the potential energy diagram will be asymmetric, and the intramolecular KIE might be expected to be determined by the relative frequency factors for abstracting a proton or a deuteron in complex I. Thus, it is interesting to notice that for these reactions the experimental k_H/k_D values are in the vicinity of $(m_D/m_H)^{1/2}$. As the reaction becomes less exothermic, and the potential energy surface more symmetric, the behavior in the second intermediate complex will become important. Thus, we propose that the branching ratio for these systems will be influenced by the equilibrium partition between IIa and IIb. Estimates of the

equilibrium isotope effect for the separated systems calculated from approximate vibrational frequencies yield values ranging from 0.52 to 0.71.[9] These values are, interestingly enough, close to the limiting values observed for the *inverse* isotope effect in near-thermoneutral or endothermic reactions. That appreciable scrambling can take place in complexes like IIa and IIb of endothermic reactions has been recently shown by DePuy[10] for systems similar to those studied in the present work.

We believe that the present results open up a wide range of applications of isotope effects in mechanistic studies of ion–molecule reactions.

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Preparation of Vinblastine, Vincristine, and Leurosidine, Antitumor Alkaloids from *Catharanthus* spp. (Apocynaceae)

Sir:

Antitumor alkaloids of the vinblastine group have been the subject of numerous chemical, biological, pharmacological, and clinical studies for the past 20 years. Efforts to achieve the synthesis of this type of compound culminated in 1974 when we discovered a new method for coupling the two obvious precursors of the vinblastine-type alkaloids, i.e., catharanthine (**1**) and vindoline (**2**)[1a,b] leading to $\Delta^{15'(20')}$-20′-deoxyvinblastine (**3**, anhydrovinblastine). We also disclosed a strategy to be used to synthesize compounds of this class, for example, vinblastine (**4**), vincristine (**5**), leurosidine (**6**), and leurosine (**7**). Several other research teams subsequently investigated this method of coupling.

Two theoretical approaches can be considered for the preparation of these bisindole alkaloids from **1** as starting material.

In the first method which has been used to prepare the bisindole alkaloids **4**, **5**,[2] and **7**,[3,4] carbon atoms C_{15} and/or C_{20} of **1** are functionalized *before* using the coupling reaction. Such an approach is not very efficient, and side reactions often occur

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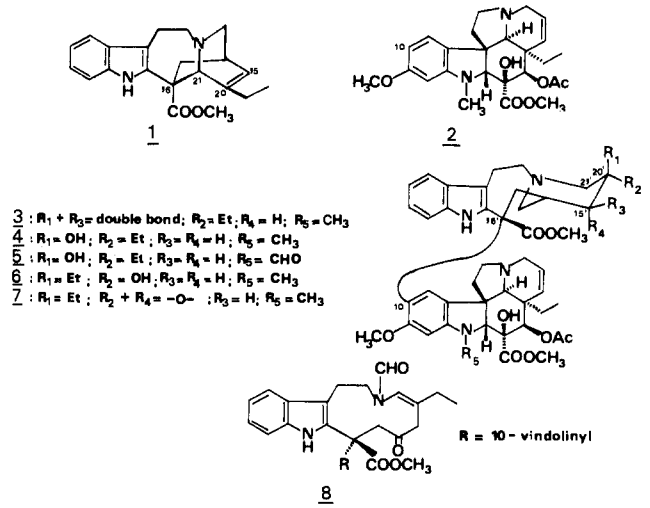


owing to the competitive fragmentation between C_5 and C_6.[5-7]

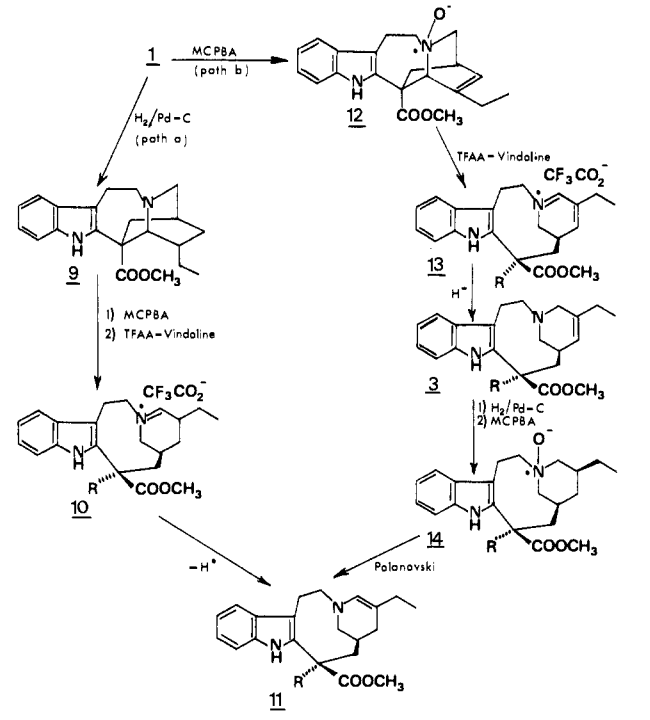
Our biogenetic approach[1c,8] for the preparation of vinblastine-type compounds takes advantage of several favorable stereoelectronic factors for direct functionalization of the $\Delta^{15'(20')}$ double bond of **3** at positions $C_{15'}$ and/or $C_{20'}$. Using this approach, we have been able to prepare various "dimeric" alkaloids such as, inter alia, **6**,[9] **7**,[3,8] catharine (**8**),[8,10] etc.

It is worthy of note that this biogenetic approach has been recently verified by in vivo experiments performed by several groups.[11,12] However, the problem of the synthesis of vinblastine (**4**) itself, following this approach, remained to be properly solved.[2] We describe here a facile process for preparing **4** and discuss the biogenetic implications.

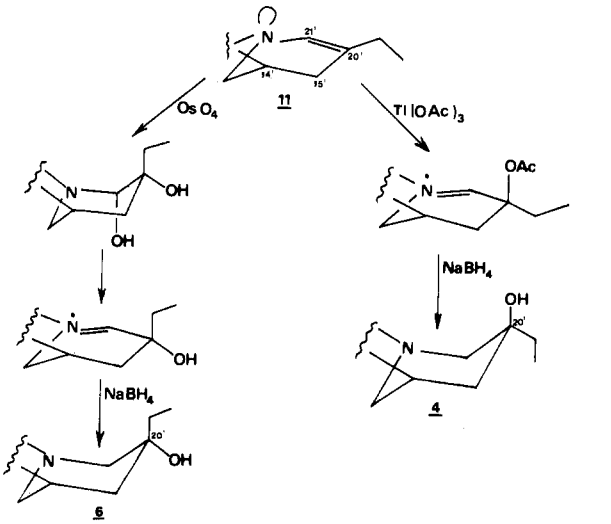
We have already described the synthesis of **6**[9] using osmium tetroxide oxidation of the unstable intermediate $\Delta^{20'}$-20′-deoxyvinblastine (**11**) which was not isolated (path a, Scheme I). We then directed our efforts toward the unequivocal preparation of enamine **11** which appeared to be a suitable intermediate for the synthesis of **4** (epimeric at $C_{20'}$ with **6**). Thus, $N_{b'}$-oxide of 20′-deoxyleurosidine (**14**, prepared quantitatively from **3** by hydrogenation and by N-oxidation) was reacted following the Polonovski reaction conditions[13] and led to the expected[14] enamine **11** (path b, Scheme I). This rather unstable compound was not isolated but directly exposed to various oxidants; treatment with thallium triacetate,[15] followed by borohydride reduction, gave rise to **4**[16] (30% from **14**). Similarly, enamine **11**, exposed to osmium tetroxide followed by borohydride reduction, led to **6** (25% from **14**).

The difference in stereoselectivity of these two reactions can easily be rationalized if we consider that the bulky osmium tetroxide attacks **11** from the less hindered α side (Scheme II). We had already observed the same selectivity during the catalytic hydrogenation of **3** leading exclusively to 20′-deoxyleurosidine.[1a,b] In the case of the preparation of **4**, compound **11** seems to react as an enamine toward the electrophilic thallium reagent.[15] The configuration of the $N_{b'}$ lone pair controls the configuration to be obtained at $C_{20'}$ (Scheme II).

Scheme I



Scheme II



Since vinblastine (**4**) is known to be easily oxidized to vincristine (**5**),[17] our approach represents also a formal synthesis of the latter.

We can now propose a biogenetic scheme for the formation of the major indole alkaloids of the vinblastine group; catharanthine (**1**) and vindoline (**2**) would be the true precursors of the conjugate immonium salt **13**. 1,2 reduction of this immonium salt would lead to anhydrovinblastine (**3**) and subsequently to leurosine (**7**). 1,4 reduction of **13** (or Polonovski-type reaction via *N*-oxide **14** as exemplified during this work) would lead to **11** and, then, to vinblastine (**4**), vincristine (**5**), etc.

This biogenetic pathway is supported by recent, but incomplete, experiments reported by Scott, Stuart, and their co-workers[11,18,19] and by our own results obtained in vitro by air oxidation. However, the true intermediacy of *N*-oxides in all of these biosynthetic processes requires further corroboration.

In vivo experiments are now underway in our laboratory in an attempt to understand the later stages of biosynthesis of this class of biologically important compounds.

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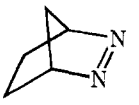
Geometrical Structure and Energetics of Closs's Diradical: 1,3-Cyclopentadiyl

Sir:

As the physical techniques (such as matrix isolation) available to organic chemists have become increasingly sophisticated, the study of diradicals has become a central focus of contemporary physical organic chemistry.[1-3] Whereas in the past diradicals have been readily postulated as reaction intermediates, the direct detection and characterization of such species is a much more recent development.[4,5]

Perhaps the most dramatic illustration of this trend concerns the diradical of bicyclo[2.1.0]pentane. The existence of this transient species has been suspected since the early 1960s, when Chesick[6] determined an activation energy of 39 kcal/mol for the reversible cis-trans isomerization of 2-methyl[2.1.0]-bicyclopentane. However, not until 1975 was there reported the first detection by physical methods of *any* 1,3 or 1,4 diradical. In this light the significance of the characterization of the 1,3-cyclopentadiyl radical[7] by Buchwalter and Closs becomes particularly apparent.

Buchwalter and Closs found that ultraviolet irradiation of matrix-isolated **1** at 5.5 K yielded a well-defined electron spin



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resonance (ESR) spectrum. Based on the fact that this spectrum persists down to 1.3 K (and on preliminary CIDNP results), they concluded that the 1,3-cyclopentadiyl diradical has a triplet ground state. Further analysis of the decay kinetics

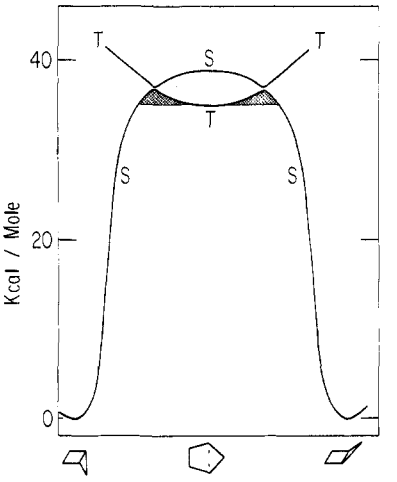

Figure 1. Schematic energetic view[7] of the isomerization between bicyclo[2.1.0]pentane and 1,3-cyclopentadiyl.

of this species suggested to Closs the schematic potential energy surface reproduced in Figure 1. This figure indicates that the triplet state of Closs's diradical is a minimum on its potential energy surface, while the lowest singlet state represents a transition state between the cis and trans bicyclopentanes. In this regard it is interesting to note that Benson-type thermochemical calculations[8] suggest a potential well of depth of 13 kcal for the singlet diradical.

It seems fair to say that very little is known about the quantitative molecular structures of triplet diradicals. Since theoretical methods have proved consistently reliable[9] in predicting the structures of the more conventional closed-shell hydrocarbons, we decided to carry out a detailed study of triplet 1,3-cyclopentadiyl. Self-consistent-field (SCF) theory was used in conjunction with a double-ζ (DZ) basis set[10] designated C(9s 5p/4s 2p) H(4s/2s). Some idea of the reliability of this may be gauged by the extensive calibrations[11] of Hehre, Pople, Radom, and Schleyer. For a sample set of 19 hydrocarbons, they find the slightly smaller but essentially comparable 4-31G basis set to predict C-C single- and double-bond distances to within an average of 0.006 and 0.020 Å of the appropriate experimental equilibrium internuclear separations. The restricted Hartree-Fock methods of Pitzer[12] were used in conjunction with the HONDO integral routines.[13] The complete theoretical treatment of a point on the C_5H_8 potential energy surface (68 contracted gaussian functions) required 3.4 h of Harris Corporation Slash Four minicomputer time.

The electron configuration for triplet 1,3-cyclopentadiyl in C_{2v} symmetry is

$$1a_1^2 2a_1^2 1b_2^2 2b_2^2 3a_1^2 4a_1^2 5a_1^2 3b_2^2 4b_2^2 6a_1^2 7a_1^2 1b_1^2 5b_2^2 8a_1^2 6b_2^2 9a_1^2 2b_1^2 - 1a_2^2 2a_2 3b_1$$

The triplet equilibrium structure was determined at the DZ SCF level of theory subject to several assumptions. All C-H distances were assumed to be 1.09 Å and each of the three methylene angles θ (HCH) was constrained to be 109°. These are certainly the least interesting aspects of the structure of Closs's diradical and are uncontroversial parameters which have relatively little effect on the predicted total energies.

Figure 2 gives the present theoretical structure of 1,3-cyclopentadiyl, and for comparison the experimentally known[14] structure of bicyclo[2.1.0]pentane. Since this is the first experimentally known cyclic diradical whose structure has been predicted theoretically, it is important to ask whether the predicted structure agrees with classical organic chemistry concepts.[15] The answer for Closs's diradical is a convincing "yes". First, the three unique C-C single-bond distances lie in the same order as that observed for bicyclo[2.1.0]pentane.[14]

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