established that each transition state had exactly one imaginary frequency. The energies of the reactants and transition states at the SCF optimized geometries[13] were recalculated with the inclusion of electron correlation at the MP2 level of theory,[14] and the transition-state geometries were reoptimized at this level of theory. These calculations were performed with the Gaussian 86 package of ab initio programs.[15] The SCF and frozen core MP2 (FC-MP2) activation energies, calculated at the SCF 3-21G optimized geometries, are given in Table I, along with the SCF and MP2 optimized, interallylic, C–C bond lengths (R) in each transition state.

Because of the flatness of the potential surface for the transition state along R, the optimized value of R can vary significantly with the type of calculation. For example, as first found by Dewar and Healey,[16] the MP2 3-21G value for R in **1**[17] (Table I) is 0.16 Å shorter than the CAS-MCSCF value.[1] In order to investigate the effect of electron correlation on the optimized transition-state geometries for **1–3**, using a variational instead of a perturbational technique, partial CI calculations were performed at three different values of R. All other geometry parameters were optimized at the SCF level (in C_{2h} symmetry for **1** and **2** and in C_i symmetry for **3**) at each value of R. The CI calculations involved all single and double excitations into the virtual orbitals (51 in **1** and 71 in **2** and **3**) from all the MOs (four in **1** and five in **2** and **3**) with appreciable contributions from p AOs oriented parallel to the interallylic C–C bonds. The three CI energies for each transition state were then fitted to a quadratic potential in R, and the minimum was found. These partial CI calculations were performed by using MELD,[19] and the resulting values of R for **1–3** are also contained in Table I.

As shown in Table I, the optimized values of R for the three transition states are consistent with the hypothesis that the relative size of the contributions of diradical structures **b** and **c** depend on the position of the radical-stabilizing cyano groups in **1–3**. Despite the differences in the absolute values of R obtained by the three different types of calculations, the trends in the values of R are the same. All three methods find that transition state **2** has the smallest value of R and that transition state **3** has the largest. Because the potential surface for the Cope rearrangement is quite flat along the coordinate R, the interallylic bond length in the chair transition state varies strongly (by about 0.25 Å at the MP2 and partial CI levels) with the positions of the cyano substituents.

The energies in Table I are in agreement with the experimental finding[3-7] that a pair of substituents is more effective at C-2 and C-5 than at the four other carbons in stabilizing the transition state for the Cope rearrangement. The FC-MP2 value of 8.2 kcal/mol for the lowering of the activation energy by the cyano substituents at C-2 and C-5 in **2** is in reasonable agreement with the experimental value of 10.4 kcal/mol for a methyl derivative of **2**.[4] After correction for zero-point energy differences, the ratio between the FC-MP2 values for the activation-energy lowering by the cyano substituents at C-1 and C-4 in **3** and at C-2 and C-5 in **2** is 0.24. This compares quite well with the experimental ratio of 0.28 for pairs of phenyl substituents at these two sets of carbons.[7]

Although cyano substituents at C-2 and C-5 substantially stabilize the Cope transition state and, in agreement with the inference drawn by Conrad and Gajewski, cause its geometry to alter in the direction expected for diradical structure **2b**, it is to be emphasized that **2** is not a diradical. This is indicated by the optimized values of R for **2** and confirmed by analysis of its CI wave function. The ratio of the squares of the two largest coefficients in the CI wave function for **2** is only 0.024, which is approximately 40 times less than the ratio of near unity that is expected in a true diradical.[20]

Acknowledgment. We thank the National Science Foundation for support of this research and for a grant that made possible the purchase of a Convex C-2 computer, on which some of these calculations were performed at the University of Washington. We also thank the San Diego Supercomputer Center for a generous grant of time on the Cray XMP-48 and Professor M. J. S. Dewar for providing us with a copy of AMPAC.

Supplementary Material Available: Structures showing SCF optimized geometries for transition states **1–3** and for the corresponding 1,5-hexadiene reactants and MP2 optimized geometries for **1–3** (9 pages). Ordering information is given on any current masthead page.

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Solvent-Induced Ring Inversion in Protonated 2,3-Dihydro-1*H*-1,4-benzodiazepines

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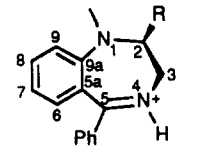
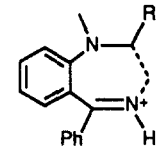
The conformation of the seven-membered ring in protonated 2,3-dihydro-1*H*-1,4-benzodiazepines is boat- or twist-boat-like in the solid state;[2] little is known about the conformations in solution. Ring inversion **1a** ⇌ **1b**, which occurs easily in the case of the unprotonated species,[3] interconverts enantiomers, making the observation of this process in principle amenable to chiroptical methods. We have found CD spectroscopic evidence that proves



1a, R = H
2a, R = CH_2NHCO- 



1b
2b

that the molecular geometry of 2-substituted derivatives is extremely dependent on solvent polarity including what we assume is a complete inversion of the seven-membered ring conformation.

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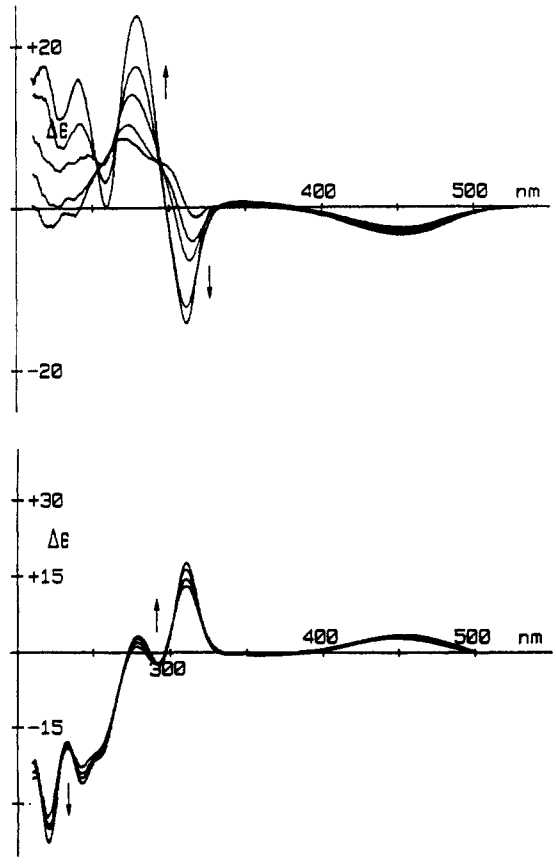


Figure 1. Top: CD spectra of **2** in EtOH/MeOH (4:1), $c = 1.04 \times 10^{-3}$ mol/L. Curves correspond to measurements at 0, −40, −80, −120, and −160 °C. Arrows indicate spectral changes with decreasing temperature. Bottom: CD spectra of **1** in THF/CH_2Cl_2 (9:1), $c = 1.04 \times 10^{-3}$ mol/L. Temperatures are 0, −40, −80, −100, and −130 °C.

Solvents employed were ethanol/methanol, 4:1, and THF/CH_2Cl_2, 9:1; protonation was effected by addition of trifluoroacetic acid (TFA). The CD spectra of **2** in the two solvents are shown in Figure 1. In EtOH/MeOH we find a long-wavelength negative band at 450 nm coinciding with a weak ($\epsilon = 3600$) UV absorption, and prominent bands at 310 and 280 nm, the latter two with a marked temperature dependence. In THF/CH_2Cl_2 the spectra have a completely different shape; most peculiar is the sign inversion of the 450-nm band, but one should note also that the spectra are much less temperature dependent in this solvent.

For structural assignments the band around 450 nm plays a pivotal role. Its sign in EtOH/MeOH correlates with the absolute configuration of the C(2) carbon, being minus for all 2*S*-configurated compounds that were available to us.[4] Sign inversion of this band in the less polar solvent THF/CH_2Cl_2 is observed throughout with two exceptions: when the phenyl ring in the 5-position is substituted in the ortho position by chlorine and when the side chain is substantially altered, e.g., to CH_2OCH_3.

In the following we present arguments based on semiempirical PM3 calculations[5] to show that the sign of the 450-nm band actually indicates the absolute configuration of the diazepine ring and that the sign inversion is a manifestation of the interconversion **a** ⇌ **b**.

Figure 2 shows computer-generated models of **2a** and **2b** with R = CH_3. These geometries represent the completely optimized

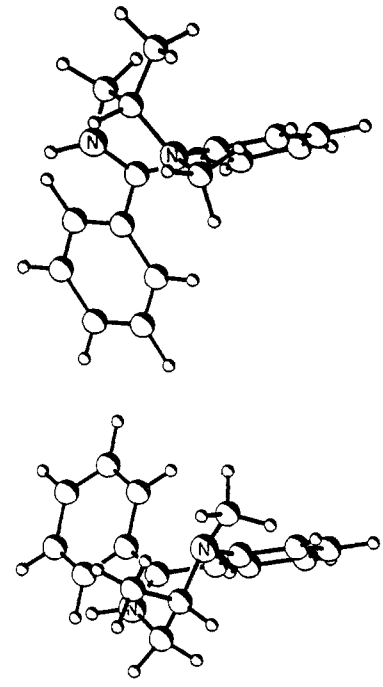
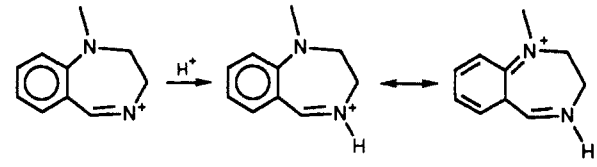


Figure 2. PM3 optimized geometries of 2(*S*)-CH_3-**2**. The conformations correspond to the two ring-inverted structures. In the upper conformation, the 2-methyl group occupies a pseudo-equatorial position; this structure is calculated to be 0.7 kcal/mol more stable than the lower, in which this group is pseudoaxial.

conformations found for the two inverting structures. They are quasi-enantiomeric: dihedral angles differ by no more than 3°, usually much less. However, the C(2) methyl group is quasi-equatorial in **2a** and quasi-axial in **2b**, which leads to a calculated energy difference of 0.7 kcal/mol in favor of the former conformation. Substitution by methyl in the 5-position does not change this small but significant bias toward the equatorial conformer.

The nature of the long-wavelength band whose intensity and position (between 400 and 460 nm) can vary considerably[3] is easy to understant qualitatively: upon protonation, the partial chromophore consisting of the condensed benzene ring and the two ortho substituents is transformed into a cyanine-type structure. This is accompanied by a pronounced bathochromic shift in the UV because of loss of double-bond fixation:



With the C=N$^+$ bond twisted out of the plane of the benzene ring, the chromophore is inherently chiral,[6] and observed rotary strengths should correlate directly with the three-dimensional structure. For geometries with a positive twist angle about the N(4)–C(5) bond, we calculate[7] negative rotary strengths for the 450-nm band regardless of any substitution at this ring and regardless also of the orientation of the benzene chromophore at C(5). This is in line with what we find experimentally: the long-wavelength band is either positive or negative, corresponding to the preferred conformation of the diazepine ring in either solvent. The conformational flexibility of the C(5) benzene ring (and possibly the side chain) shows up primarily in the temperature

(4) So far we have found no exception to this rule, which applies to six derivatives with known absolute configurations. Five more derivatives have been separated and spectroscopically analyzed, but the absolute configuration has not been assigned independently.

(5) Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 209, 221; QCPE No. 455. The structures optimized were the parent benzodiazepine, various methyl-substituted derivatives (positions 1, 2, 5, and 6), and **2**, as free bases and as protonated species. The gradient norm reached during optimization (PRECISE option) was always less than 1.

(6) For a related discussion involving 3-substituted 1,4-benzodiazepines, see: Snatzke, G.; Konowal, A.; Sabljic, A.; Blazevic, N.; Sunjic, V. *Croat. Chem. Acta* **1982**, *55*, 435.

(7) Calculations employed CNDO/S (up to 300 SDCI) on PM3 optimized geometries for energies and MOMPRO (Rauk, A.; Jarrie, J. O.; Ichimura, H. J.; Buriel, J. *J. Am. Chem. Soc.* **1975**, *97*, 5656) for moments.

dependence of the 310- and 280-nm bands.

The negative 450-nm band of the 2*S*-configurated diazepines in EtOH/MeOH suggests the preference for pseudoequatorial substitution at C(2), in accordance with our PM3 results. Ring inversion in THF/CH_2Cl_2 can be brought about by a variety of factors, the most probable ones being hydrogen bonding between N^+–H and the carbonyl group of the side chain and $\pi\pi$-stacking of the side-chain aromatic with the C(5) benzene ring. Both interactions require a pseudoaxial side chain, and both are more effective in nonpolar than in polar solvents. Moreover, they result in a rather rigid, conformationally locked geometry, which is what we see in this solvent.

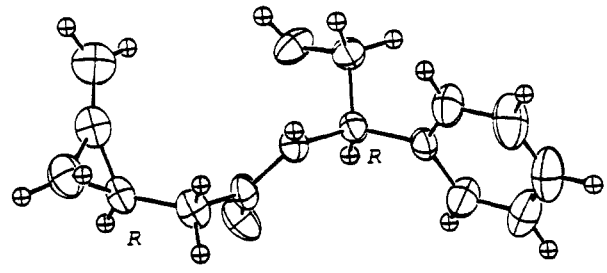


Figure 1. ORTEP drawing of the (*R*)-(−)-2-phenylglycinol amide of (*R*)-(−)-(methylenecyclopropyl)acetic acid.

Stereospecific Inactivation of the General Acyl-CoA Dehydrogenase from Pig Kidney by (*R*)-(−)-(Methylenecyclopropyl)acetyl-CoA and (*S*)-(+)-(Methylenecyclopropyl)acetyl-CoA

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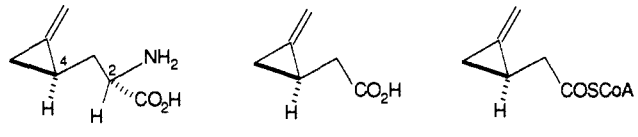
The amino acid hypoglycin isolated from the fruit of the Jamaican ackee tree (*Blighia sapida*) is metabolized in mammals to (methylenecyclopropyl)acetyl-CoA; this thioester, MCPA-CoA, elicits the biochemical derangements associated with the Jamaican vomiting sickness as it inactivates acyl-CoA dehydrogenases.[1-3]



(2*S*,4*R*)-hypoglycin (*R*)-MCPA (*R*)-MCPA-CoA

Whether the reaction of MCPA-CoA with the general acyl-CoA dehydrogenase from pig kidney (GAD; EC 1.3.99.3) is stereospecific or not remains unresolved, for the issue depends on quantitative determinations of rates of inactivation of the CoA esters of each antipode of MCPA, and such data have not previously been secured. Residual enzymic activities after inactivations by aliquots of (±)-MCPA-CoA have been reported by two groups[4,5] and compared with a third group's data for similar studies with MCPA-CoA derived from ackee fruit.[6,7] Given the sensitivity of this approach to substrate and enzyme purities and to experimental estimations of concentrations made in three different laboratories, it is not too surprising that conflicting conclusions have been reached. These attempts to resolve the issue have been limited in a more fundamental way by ignorance about the optical purity of naturally derived MCPA; a chemical correlation has established that the natural product is predominantly of *R* absolute stereochemistry,[4,8] but this correlation from (+)-hypoglycin via

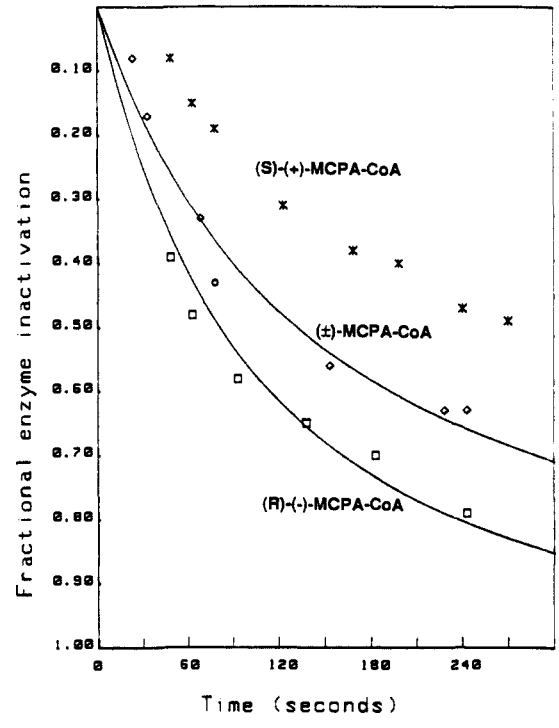


Figure 2. Loss of GAD activity (e_0, 3.1 μM) versus time for (*R*)-(−)-MCPA-CoA, (±)-MCPA-CoA, and (*S*)-(+)-MCPA-CoA (s_0, 15.5, 16.3, 15.4 μM, respectively). The theoretical curves drawn by computer are based on the Tatsunami equation[17,18] [$t = rB(\ln((1 - (1 + r)\mu(1 - x))/x))/Cs_0(1 - (1 + r)\mu) - r(\ln x)/C$, where t is time, e, e_i, and s represent concentrations of E, E_i, and S, $\mu = e_0/s_0$, r is the partitioning ratio, x is the fractional enzyme activity remaining ($1 - e_i/e_0$), and B and C are known[18] functions of rate constants] with the parameters $B = 40$, $C = 0.1$, and $r = 2.7$ ((*R*)-(−)-MCPA-CoA) or $r = 4.2$ ((±)-MCPA-CoA).

MCPA gave (+)-(*S*)-3-methylpentanoic acid of only 17% optical purity.[9]

To settle this question of stereospecificity, the acid chloride of (±)-MCPA[4] was treated with (*R*)-(−)-2-phenylglycinol and the two diastereomeric amides formed were separated by HPLC on a Nucleosil 50-5 column using 3:2 ethyl acetate/2,2,4-trimethylpentane as eluant.[10,11] Slow crystallization of the first amide from 1:2 ethyl acetate/2,2,4-trimethylpentane gave monoclinic plates, mp 89–92.5 °C. The X-ray crystal structure determination[12] showed that the molecule crystallized in the

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