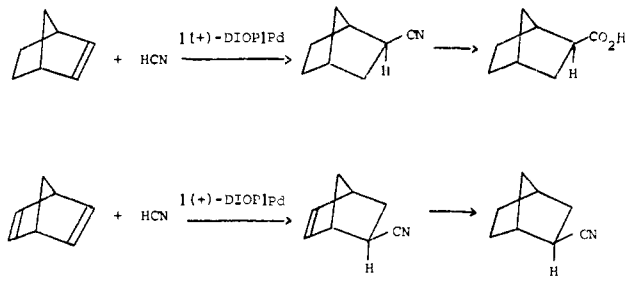
Scheme I



2-*exo*-cyanonorborn-5-ene (1.5 g, 40% based on HCN), $[\alpha]_D$ −3.0°, which on hydrogenation gave 2-*exo*-cyanonorbornane, $[\alpha]_D$ −2.1°. Thus the (1*R*,2*R*,4*S*) enantiomer predominated in the reaction mixture and was in ~17% enantiomeric excess. Reaction of benznorbornadiene gave the exo nitrile, $[\alpha]_D$ −11.3°, which was reduced to the corresponding amine, $[\alpha]_D$ −6.5°. The amine was shown to be a 2:1 mixture of enantiomers by the use of NMR chiral shift reagents. Attempted reaction of 7,7-dimethylnorbornene with hydrogen cyanide under these conditions led to the recovery of alkene, suggesting that the reaction is very susceptible to steric hindrance.

When the [(+)-DIOP]Pd was used to catalyze the addition of hydrogen cyanide to terminal alkenes, e.g., dec-1-ene and pent-1-ene, the anti-Markownikoff, terminal nitriles predominated in the product mixture by ratios of ~7:1:

$$RCH{=}CH_2 + HCN \xrightarrow{\text{(DIOP)Pd}} \underset{7}{RCH_2CH_2CN} + \underset{1}{RCH(CN)CH_3}$$

This regioselectivity compares very favorably with those quoted in many patents concerning hydrogen cyanide addition to terminal alkenes.[6,7]

The [(+)-DIOP]Pd was prepared by two independent routes. Reduction of palladium(II) chloride with hydrazine hydrate in dimethyl sulfoxide solution in the presence of (+)-DIOP or reduction of [(+)-DIOP]$PdCl_2$ with sodium borohydride in acetone solution in the presence of DIOP gave in each case an air-sensitive yellow solid, $[\alpha]_D$ −55°. This yellow solid material had previously been prepared by Trost but not fully characterized.[3] The compound showed ^1H NMR absorptions at δ 7.4 and 7.1 (m, Ph, 20 H), 3.26 (br s, H-2, -3, 2 H), 2.64 (d, H-1′, -4′, 2 H), 1.71 (dd, H-1, -4, 2 H), and 1.12 ppm (s, Me, 6 H) with $J_{1,1'} = 12.9$, $J_{1,2} = 8.0$, and $J_{1',2} < 3$ Hz. However, in addition to the above absorptions samples prepared in Me_2SO showed an absorption at δ 2.59 ppm and samples prepared in acetone showed an absorption at δ 2.16 ppm suggestive of involvement of solvent molecules as ligands. Most of the solvent could be removed by allowing the material to stand for extended periods under high vacuum. Two separate samples analyzed correctly for [(+)-DIOP]Pd. Mass spectral data suggested that the compound was not monomeric.

The ^{31}P spectrum of the compound was temperature variable showing a single resonance at 0.7 ppm (from external H_3PO_4) which broadened and separated into two singlets below −69 °C corresponding to a dynamic process with $\Delta G^{\ddagger} \approx 37$ kJ mol^{-1} at the coalescence temperature. A dynamic process with $\Delta G^{\ddagger} = 48$ kJ mol^{-1} has been reported for the ^{31}P NMR spectrum of the platinum compound, [(+)-DIOP]$_2$Pt.[8] The origins of the dynamic behavior in the platinum compound were attributed to conformational exchange between the two different seven-membered rings. In view of the different formulations for the palladium and platinum compounds, further investigation is clearly necessary.

The diphosphinoethanes, "diphos" ($Ph_2P(CH_2)_2PPh_2$) and "chiraphos" ($Ph_2PCH(CH_3)CH(CH_3)PPh_2$),[9] gave palladium compounds which analyzed for (diphosphine)$_2$Pd. These compounds showed no catalytic activity for HCN addition, and the compound $(Ph_2P(CH_2)_3PPh_2)_2Pd$ showed very reduced catalytic activity relative to the DIOP compound.

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Peptides and Their Retro Enantiomers Are Topologically Nonidentical

Sir:

One approach to the design of biologically active peptide analogues relies on topochemical analysis. A hypothesis which arose from such considerations was that of Shemyakin concerning retro-enantiomeric peptides in which the sequence is reversed and the chirality at each residue is inverted relative to parent peptides.[1] This theory was first advanced for cyclic peptides and stated that a peptide and its retro enantiomer "are very similar topologically, differing only by reversed arrangement of the atoms in the amide groups". This analysis may be extended to linear peptides if the end-group problem (reversal of amino and carboxyl termini) is solved, but it must fail for proline-containing peptides. These problems have been considered in detail by Shemyakin[1] and later by Morley[2] and Goodman.[3]

Retro-enantiomeric peptides are especially attractive synthetic targets since, if it should prove that only the side chains are important in the interaction with a biological receptor, these analogues should elicit a response similar to the parent compound. Increased resistance to enzymatic degradation would result because most peptidases are specific for L-amino acids.

Although some small degree of dissimilarity of topology between the isomers has been recognized,[4] these small differences appear to have been generally thought to be insignificant. Thus, the retro-enantiomer approach has received a great deal of attention and has been applied in a number of instances. Interestingly, however, it apparently has been successful in only a limited number of cases.[5,6]

The difficulties in attaining successful applications of the retro-enantiomer rationale led us to examine further the basic concept. One explanation of these results, of course, is that the peptide backbone does interact with the biological receptor and, therefore, cannot be neglected. A second answer might be found in a change in conformation due to a new set of intramolecular interactions from reversal of the peptide sequence. Reversal of the direction of the peptide bonds assigns values for the C′N-C$^{\alpha}$C′ torsional angle (ϕ) to the NC$^{\alpha}$-C′N

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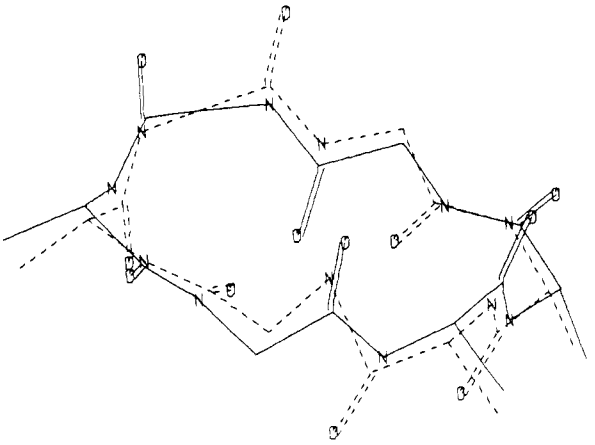

Figure 1. Computer superposition of c-(Ala-Ala-Gly-Gly-Ala-Gly) (solid lines) with its retro enantiomer (dashed lines) using a least-squares fit of six α carbons.

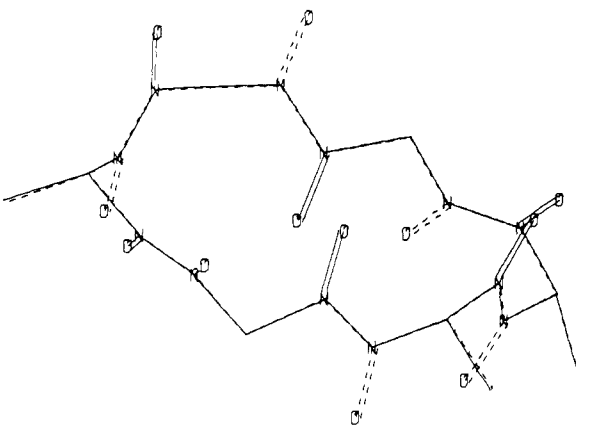

Figure 2. Computer superposition of c-(Ala-Ala-Gly-Gly-Ala-Gly) (solid lines) with its retro enantiomer modified as described in text to improve fit (dashed lines).

torsional angle (ψ) and vice versa. Inspection of a Ramachandran plot shows that this transposition can lead to sterically disallowed conformations, and, in such cases, conformational change would be expected. Evidence of such a possibility was recently derived from conformational energy calculations on *retro-all*-D-methionine enkephalin.[7] In the hope of finding some means of correcting any conformational changes through further structure modification, we have initiated analysis of the problem in a rigorous manner using computer superposition of structures. We have found that, contrary to common interpretation of the hypothesis, side-chain topology is not maintained between a peptide and its retro enantiomer, even if it is assumed that no serious steric interactions exist to cause a change in conformation.

In order to make comparisons by computer matching, a well-defined starting structure and a rigorous definition of its transformation into the retro enantiomer are required. We chose to do this analysis using the X-ray structure of c-(Ala-Ala-Gly-Gly-Ala-Gly) (**1**) as a starting point since the bond lengths, bond angles, and dihedral angles necessary to display the molecular model in our computer graphics system[8] have been reported.[9] The retro enantiomer c-(Gly-D-Ala-Gly-Gly-D-Ala-D-Ala) (**2**) was created by inputting the amino acids in reverse order relative to the starting structure. The same structural parameters were employed except that backbone dihedral angles were applied in reverse order and the negatives of side-chain dihedral angles were used. The result of these operations is to reverse the direction of the amide bonds and invert the chirality of the α carbons as specified by the retro-enantiomer hypothesis.

The two structures were then superposed using a least-squares fit of the six α carbons. This match is shown in Figure 1 with structure **1** solid and structure **2** dashed lines. The topology of the two structures is similar, but clearly not identical. The existence of "some degree of nonequivalence in the attachment of the side chain" has been recognized;[4] however, the best fit still leaves an average deviation in distance between the matched atoms of 0.35 Å. The side-chain methyls match up even more poorly with the average deviation being 0.50 Å. When the structures are superposed using a least-squares fit of the side-chain methyl carbons, the average deviation in distance between the matched atoms is 0.20 Å and between the α carbons is 0.39 Å. One pair of α carbons has a separation of >1.1 Å. The failure to obtain the expected match forced us to explore further variants in order to create a transformation in which the side chains attain topological identity. In the comparison shown in Figure 1, *dihedral* angles in the retro-enantiomer peptide backbone have been given the same values as the corresponding backbone *dihedral* angles of the starting structure to which they are matched. It appeared that, to further improve the fit of the two structures, *bond* lengths and *bond* angles of the retro-enantiomer backbone would also need to have the same values as those with which they are matched in the starting structure. Most critical are the bond lengths and the bond angles involved in the connection of the amide units to the α carbons. The retro enantiomer was modified accordingly and matched to the parent structure. As shown in Figure 2, the correspondence in side-chain topology is now excellent, and the only significant difference between the two structures is the reversal of peptide backbone directions as predicted by Shemyakin. The average deviation in distance between the six α carbons is 0.02 Å and between the side-chain methyls 0.08 Å.

This artificially created version of the retro enantiomer which provides the desired fit goes to the heart of the problem of the hypothesis, since this structure cannot exist. Bond lengths and bond angles were given values which do not occur. Thus, unallowed changes were required to make the retro enantiomer match the starting cyclic peptide. For example, C^{α}–N bonds having a usual length of 1.45 ± 0.02 Å were assigned the value of C^{α}–C′ bond lengths (1.53 ± 0.01 Å)[10] and vice versa. It is the cumulative effect of these small differences in structural parameters between a peptide and its retro enantiomer which prevent the good match of the side chains as predicted by Shemyakin.

This analysis is applicable to any peptide and leads to the conclusion that the usual rigorous interpretation of the retro-enantiomer hypothesis is not valid. The actual differences between a peptide and its retro enantiomer are such that different side-chain topology must exist which may also result in different conformations. In spite of these limitations, successful application of the retro-enantiomer hypothesis may be possible through fortuitous or designed matching of part or all of the general shape of the molecules. Three factors must be taken into account, therefore, in any conclusion based on the biological activity of retro enantiomers. First, contrary to one of the assumptions of the hypothesis, interactions may occur between the peptide backbone and the biological receptor. Second, reversal of the backbone may produce new intramolecular interactions which result in a change in conformation. Finally, even if it were possible to neglect the first two points, our study has shown that there are innate differences in side-chain topology between the retro enantiomer and the parent peptide.

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A New View of the Dynamics of Singlet Cis–Trans Photoisomerization

Sir:

Cis–trans photoisomerization around carbon–carbon double bonds has long been a subject of experimental investigation (see, for example, ref 1 and 2) and theoretical interpretation.[3-6] There is overwhelming evidence that singlet photoisomerization plays an important role in many systems, including the visual pigment; yet the dynamics of the process are not well understood. According to the customary viewpoint, radiationless transitions to the cis and trans ground states occur from a twisted "common intermediate" in which the vibrational energy levels are in thermal equilibrium.[3,4,7,8] This picture cannot describe cases when the lifetime of the twisted excited state is too short for vibrational equilibration[6,9] (see note 10). The semiclassical trajectory approach[5,6] might be more adequate for studies of the dynamics of cis–trans photoisomerization. Using this approach to study photoisomerization of alkenes and polyenes, we have found that *the surface crossing probability for a twisted double bond in its excited singlet state is much larger than previously thought, leading to a new dynamic picture of singlet cis–trans photoisomerization.*

Figure 1 shows typical ground and first excited singlet state potential energy surfaces as functions of the torsion angle ϕ of the isomerized bond. The photoisomerization process (Figure 2) involves excitation to the upper surface at $\phi \simeq 0$, rotation about the isomerizing bond to $\phi \simeq \pi/2$, oscillations in the excited state minimum, and surface crossing to the ground state with conservation of the sense of the torsional momentum.[6,11,12] The surface crossing probability per pass through the excited-state minimum is given[6] by

$$\theta = \left[\int_{\text{pass}} \dot{a}_0(t)\mathrm{d}t\right]^2$$

$$\int \dot{a}_0(t)\mathrm{d}t = \int a_1(t)\sigma(\phi)\dot{\phi}\exp\left\{-\frac{i}{\hbar}\int_0^t [E_1(\phi(t')) - E_0(\phi(t'))]\mathrm{d}t'\right\}\mathrm{d}\phi/\dot{\phi} \quad (1)$$

where $|a_i(t)|^2$ is the probability that the system is in the ith electronic state at time t and the initial conditions for the integration are $a_1(0) = 1, a_0(0) = 0$. ψ_i and E_i are the electronic wave function and adiabatic potential surface of the ith electronic state and $\sigma(\phi) = \langle\psi_1|\partial\psi_0/\partial\phi\rangle$ is the singlet–singlet nonadiabatic coupling. If θ is small, the quantum yield (Y) cannot be significantly greater than ½ (Figure 2). If θ is the same on each pass, then one obtains[13]

$$Y = (1-f)\theta[1 + (1-\theta)^2 + (1-\theta)^4 + \ldots] = (1-f)/(2-\theta) \quad (2)$$

where f is the fraction of molecules that never reach the crossing region owing to competing processes (e.g., fluorescence and radiationless transitions from the minimum at $\phi \simeq 0$).

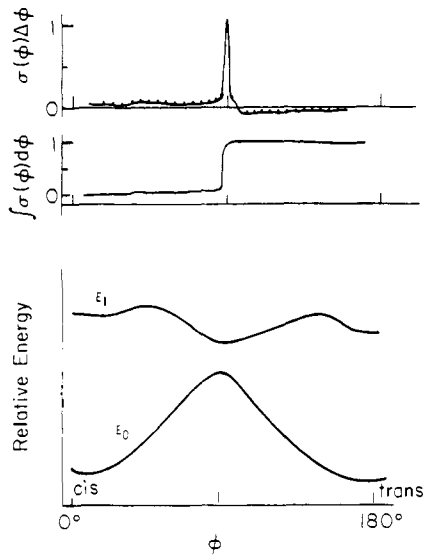

Figure 1. (Bottom) Energy diagram showing the ground and first excited singlet states of an alkene or polyene. E_0 and E_1 are the adiabatic energy surfaces as functions of the double-bond torsional angle ϕ. (Top) The nonadiabatic coupling between the two states, $\sigma(\phi)$, and its integral which determine the transition probability to the ground state. $\sigma(\phi)$ is presented multiplied by $\Delta\phi$ where $\Delta\phi$ is the increment used in numerical evaluation of $\sigma(\phi)$. These values of $\sigma(\phi)$ were calculated for rotation about the 11–12 bond of retinal.[13]

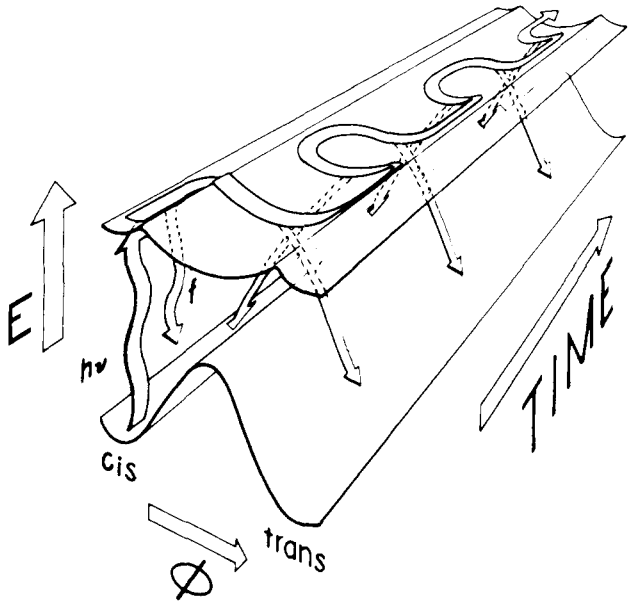

Figure 2. Photoisomerization dynamics in the region $\phi \simeq \pi/2$ showing the relationships between surface crossing probability and cis–trans quantum yield. The molecule oscillates in the excited-state torsional minimum. Transitions which occur while ϕ is increasing result in trans product, while decreasing, cis. If the transition probability per oscillation is small, many oscillations will take place in this region and the probabilities of crossing in each direction will be ~0.5. If the transition probability is large, more product than reactant will result from the molecules reaching this region. Note that some fraction (f) does not reach the crossing region.

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