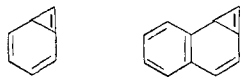

i ii

is observed at 1760 cm^{-1} (i and ii: unpublished observations of J.-P. LeRoux and P. R. West). The assignment of the 1810-cm^{-1} band to an allene has no precedent. The shift to lower frequency is, however, in accord with the frequency shift observed in the ketenimine system (1).[1] The 850-cm^{-1} band is a standard allene C–H deformation mode. Replacement of the diazomethyl hydrogen in 3- and 4-diazomethylpyridine produced deuterated derivatives of 7 which are not identical. The 1810-cm^{-1} absorption is shifted to 1800 cm^{-1} in each case. This shift is reasonable for deuterated allenes but far below the 50-cm^{-1} shift characteristic of detuerated cyclopropenes (G. L. Gloss, *Adv. Alicycl. Chem.*, **1**, 53 (1966)).

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Effects of Electric and Magnetic Fields on Prochiral Chemical Reactions: Macroscopic Electric and Magnetic Fields Can Cause Asymmetric Synthesis[1]

Sir:

We address the question of whether the application of uniform and constant electric and magnetic fields to an achiral or racemic (prochiral) reaction mixture can lead to asymmetric synthesis of products.

The literature contains one report of asymmetric syntheses in the presence of magnetic and presumed electric fields.[2] Small optical rotations (maximum 0.024°) were obtained for various reactions and field orientations. In spite of the fact that the macroscopic electric field must have been zero[3] in the reactions conducted by Gerike, the theoretical possibility of applied field effects on prochiral reactions is quite interesting.

In answer to the question of the theoretical possibility of such field effects on asymmetric synthesis, Mead, Moscowitz, Wynberg, and Meuwese have presented a theorem[4] which shows that, in the presence of constant and uniform electric and magnetic fields, a molecule M and its enantiomer M* have states of the same energy. Consequently, they conclude that asymmetric synthesis under the specified conditions is impossible. Their argument is based on the application of two symmetry operations to the entire system (reaction and applied fields): a plane of reflection, σ, and time reversal, T. The electric field, **E**, and magnetic field, **B**, have arbitrary relative directions. Successive application of σ (chosen to contain **E** and **B**) and T have the following effect:

$$[\mathrm{M}, \mathbf{B}, \mathbf{E}] \xrightarrow{\sigma} [\mathrm{M}^*, -\mathbf{B}, \mathbf{E}] \xrightarrow{T} [\mathrm{M}^*, \mathbf{B}, \mathbf{E}] \quad (1)$$

Thus, the net effect of the two operations is to transform M into M*, showing that the two enantiomers have (stationary) states with the same set of energy levels in the presence of the fields.

The conclusion that such fields cannot induce asymmetric synthesis is based on the condition of complete thermodynamic equilibrium, whereby, in accordance with the above theorem, equal concentrations of enantiomeric products, P, and P*, are attained. In many systems, however, the actual concentrations of reaction components may be kinetically, rather than thermodynamically, controlled. This is the case, in particular, if given reactants can produce different products by reaction paths having different activation energies, and if equilibrium strongly favors product formation. Such reactions can essentially go to "completion" without reaching complete thermodynamic equilibrium. In these cases the theorem above does not apply.

We will show below that parallel **E** and **B** fields, which are constant and uniform, can differentially affect the rate constant for the formation of enantiomeric products, P and P*, from an optically inactive mixture of reactants. The argument depends on the existence of a current density (or magnetic moment) in the transition states which are precursors to products. We denote the current density by **j** and the precursor molecule with current density by A(**j**). Now consider the effect of the operations σ and T as defined above:

$$[\mathrm{A}(\mathbf{j}), \mathbf{B}, \mathbf{E}] \xrightarrow{\sigma} [\mathrm{A}^*(\mathbf{j}^*), -\mathbf{B}, \mathbf{E}] \xrightarrow{T} [\mathrm{A}^*(-\mathbf{j}^*), \mathbf{B}, \mathbf{E}] \quad (2)$$

The symbol $\mathbf{j}^*$ represents $\sigma\mathbf{j}$, the reflected current density. This result shows that molecule A with current density **j** has the same energies in the fields as does molecule A* with current density $-\mathbf{j}^*$.

Let us assume that A(**j**) is the precursor to product P and that A*($\mathbf{j}^*$) is the precursor to the enantiomeric product P*. While it is true that A(**j**) and A*($-\mathbf{j}^*$) have the same energy, it follows that, in general, A(**j**) and A*($\mathbf{j}^*$) do not have the same energy if **j** and $\mathbf{j}^*$ are not superimposable in space. Therefore, at thermal equilibrium, the concentrations of the two species will differ and, consequently, so will the rates of formation of P and P*.

The current density in the precursor molecule may be intrinsic to the molecule (such as a stationary magnetic moment) or it may be induced by the applied fields or by molecular interactions. Induced currents may be due either to adiabatic (stationary) response or to nonadiabatic (transient) response of the molecule. Nonadiabatic responses may be particularly important in transition states.

The adiabatic response to the applied field **B** is of particular interest. Formulation of the second-order response tensor, $K^{(2)}$, for the response of **j** to **B** shows[5] that, for molecules having no current density in the absence of the field, $K^{(2)} = 0$. This implies that, for such molecules, $\Delta\mathbf{j}(\mathrm{A},\mathbf{B}) = \Delta\mathbf{j}^*(\mathrm{A},-\mathbf{B}) = \Delta\mathbf{j}^*(\mathrm{A},\mathbf{B}^*)$, where $\Delta\mathbf{j}(\mathrm{A},\mathbf{B})$ is the current response of molecule A to **B** and $\mathbf{B}^* \equiv \sigma\mathbf{B}$. However, it follows that $\Delta\mathbf{j}^*(\mathrm{A},\mathbf{B}^*)$ is identical with $\Delta\mathbf{j}(\mathrm{A}^*,\mathbf{B})$; therefore,

$$\Delta\mathbf{j}(\mathrm{A},\mathbf{B}) = \Delta\mathbf{j}(\mathrm{A}^*,\mathbf{B})$$

which shows that the adiabatic current response of A and A* are the same. Consequently, if the unperturbed A has no current density, adiabatic current response to **B** cannot, of itself, contribute to asymmetric synthesis.

The above argument reduces the number of possible sources of effective current density to (1) the presence of an intrinsic stationary magnetic moment and (2) the nonadiabatic response of a (transient) magnetic moment.

An example of the first is a precursor molecule A having only one plane of symmetry and a magnetic moment perpendicular to the symmetry plane. The magnetic moment could be due to spin. There are two possible species, denoted by A(**j**) and A($-\mathbf{j}$), having opposite magnetic polarizations relative to the molecular plane. One is produced from the other by the successive operations of reflection and time reversal. In the absence of magnetic interactions, A(**j**) and A($-\mathbf{j}$) are degenerate. Distortions of molecule A which destroys the symmetry plane lead to P and P* depending on the direction of distortion. If the electric field influences the direction of distortion (be-

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cause of formation of an electric dipole moment), then it follows that the relative directions of **E** and **B** can be so chosen that A(**j**) leads preferentially to P and A(−**j**) leads preferentially to P*. Obviously, an equal mixture of the two precursor species results in a racemic mixture of P and P*. However, if one of the species, e.g., A(**j**), can be preselected by some mechanism, then asymmetric synthesis becomes possible, in principle. In many cases the degree of asymmetric synthesis would be reduced, in practice, by short magnetic moment relaxation times.

Examples of the second source of current density are (a) nonadiabatic current response to the applied fields and (b) nonadiabatic current response to intermolecular interaction, as with a bimolecular transition state. However, these are mentioned only as possible sources of transient currents in molecules. Whether or not they are capable of contributing significantly to asymmetric synthesis remains to be determined.

The above discussion has established the point that, in principle, it is possible for constant and uniform electric and magnetic fields to modify the kinetics of a prochiral reaction to permit asymmetric synthesis. The magnitude of this effect, of course, depends on the particular mechanism and system. However, to provide a basis for order of magnitude estimates, we have calculated the kinetic effect for transition states having electric and magnetic moments for the following set of parameters: electric field, 10^3 V/cm; magnetic field, 10^4 G; transition state electric dipole moment (μ), 1 eÅ; transition state magnetic moment (**m**), 1 B_μ. For parallel **E** and **B** and for parallel electric and magnetic moments, application of the Langevin equation gives the ratio of rate constants

$$k_P/k_{P^*} \approx \exp\left(\frac{1}{3}\frac{\mu \mathbf{E}}{kT}\frac{\mathbf{mB}}{kT}\right)$$

This corresponds to an enantiomeric excess of 0.3 ppm at 298 K, which suggests that for most systems the degree of asymmetric synthesis is expected to be very small.

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References and Notes

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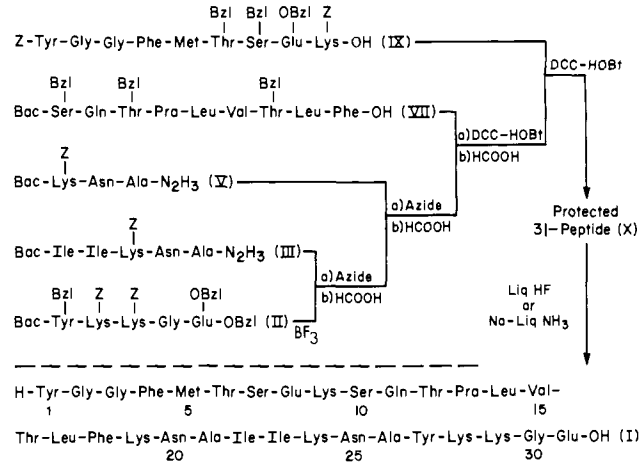
A Synthesis of Human β-Endorphin in Solution

Sir:

β-Endorphin (β-EP)[1] has been isolated from pituitary glands of several mammalian species including man, and characterized chemically and biologically. It is a 31-residue peptide whose amino acid sequence was noted to be identical with that of β-lipotropin-(61–91). β-EP possesses potent morphine-like analgesic activity by intracerebroventricular or intravenous injection in laboratory animals. Certain behavioral changes caused by β-EP in experimental animals are of considerable current interest; see ref 2 for a review. Several solid-phase syntheses of human β-EP have been reported.[3] This communication describes a solution synthesis of human β-EP (I) via segment condensation and maximum protection of side-chain functionalities by benzyl-type groups, as shown in Scheme I. Homogeneous β-EP, indistinguishable from authentic material[2,4] in physicochemical and biological characteristics, was obtained in a single reversed-phase preparative liquid chromatographic step after protecting group cleavage.

Scheme I. Synthetic Route to Human β-EP (I)



For the synthesis of the COOH-terminal-protected decapeptide Boc-Ile-Ile-Lys(Z)-Asn-Ala-Tyr(Bzl)-Lys(Z)-Lys(Z)-Gly-Glu(OBzl)-OBzl, IV, the protected pentapeptide hydrazide III, in DMF, was converted[5] to the azide and coupled with the pentapeptide amine obtained from II by Boc group cleavage with BF_3–OEt_2 in AcOH.[6] Decapeptide IV had mp 239–241 °C dec, $[\alpha]^{25}_D$ −18.5° (*c* 0.99, Me_2SO), diagnostic AAA[7].$Asp_{1.0}$, $Glu_{1.0}$.[8] To prepare the 13-peptide, Boc-Lys(Z)-Asn-Ala-Ile-Ile-Lys(Z)-Asn-Ala-Tyr(Bzl)-Lys(Z)-Lys(Z)-Gly-Glu(OBzl)-OBzl, VI, the protected tripeptide azide prepared[5] from Boc-Lys(Z)-Asn-Ala-N_2H_3, V (mp 177–180 °C; $[\alpha]^{25}_D$ −14.9° (*c* 1, DMF)), was coupled in a DMF–Me_2SO solution (1 h at −15 °C and 4 days at 4 °C) with the decapeptide amine, resulting from treatment of IV with HCOOH for 3.5 h at 25 °C. The 13-peptide, VI, was obtained in 83% yield, mp 257–259 °C dec, $[\alpha]^{25}_D$ −24.8° (*c* 1, Me_2SO). The 22-peptide, Boc-Ser(Bzl)-Gln-Thr(Bzl)-Pro-Leu-Val-Thr(Bzl)-Leu-Phe-Lys(Z)-Asn-Ala-Ile-Ile-Lys(Z)-Asn-Ala-Tyr(Bzl)-Lys(Z)-Lys(Z)-Gly-Glu(OBzl)-OBzl, VIII (mp 283–290 °C dec; $[\alpha]^{25}_D$ −23.8° (*c* 0.49, Me_2SO); AAA, $Val_{0.98}$,$Gly_{1.00}$), was synthesized in 86% yield by dicyclohexyl carbodiimide-hydroxybenzotriazole (DCC–HOBt) mediated preactivation coupling[9] (2 hr at 0 °C, 3 days at 25 °C) of the protected nonapeptide acid VII (mp 205–207 °C, $[\alpha]^{25}_D$ −20.1° (*c* 1, DMF)) and the 13-peptide amine, prepared from VI by Boc group cleavage (3.5 h, 25 °C) with HCOOH. To prepare the final protected 31-peptide, Z-Tyr-Gly-Gly-Phe-Met-Thr(Bzl)-Ser(Bzl)-Glu(OBzl)-Lys(Z)-Ser(Bzl)-Gln-Thr(Bzl)-Pro-Leu-Val-Thr(Bzl)-Leu-Phe-Lys(Z)-Asn-Ala-Ile-Ile-Lys(Z)-Asn-Ala-Tyr-(Bzl)-Lys(Z)-Lys(Z)-Gly-Glu(OBzl)-OBzl, X (82%; mp 273–276 °C dec; $[\alpha]^{25}_D$ −36.4° (*c* 0.5, *i*-C_3F_6HOH); AAA, $Met_{1.1}$, $Val_{0.93}$), the DCC–HOBt preactivation coupling[9] (1 h at 0 °C, 3 days at 25 °C) of the protected nonapeptide acid IX (mp 227–231 °C dec, $[\alpha]^{25}_D$ −3.2° (*c* 1, DMF)) and the 22-peptide amine, produced from VIII by HCOOH treatment (3.5 h at 25 °C), had to be carried out in a 1:1 mixture of DMF and phenol[10] owing to the limited solubility of the 22-peptide

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