Amino Acids (1992) 2: 97–102

Amino
Acids

A model for the chiral recognition of L and D amino acids by helicoidal systems

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Summary. The interaction between a helix and an amino acid molecule is determined on the basis of semi-empirical potentials including Lennard-Jones, electrostatic, induction and hydrogen bond contributions. Calculations are performed for various values of the helix characteristics which schematize helicoidal polysaccharides (cellulose, cellulose derivatives...). The helix configuration acts as a chiral revealer as it frozes the amino acid inside its cavity. The chiral discriminatory ratio is maximum for similar sizes of the cavity and of the analyte.

Keywords: Amino acids – Helicoidal polymer phase – Amino acid molecule – Chirality – Chiral revealer

Introduction

High performance liquid chromatography is a method of choice for the separation of enantiomers, [7, 10] and more particularly that based on the selective interactions with chiral stationary phases [7, 9]. Chiral recognition can occur through hydrogen-bonding, dipole stacking, charge transfer in donor-acceptor type phases, [12] through formation of complexes with metal ions in ligand exchange phases [4] or through a combination of hydrophobic and polar or ionic interactions in protein phases [1, 5]. But other chiral phases lead to enantiomer separation due to the structural conformation of their chiral monomers. For instance, the chirality of cellulose esters arises [6, 8] from their helicity and the enantiomer resolution involves discriminatory attractive interactions for the analyte inclusion into the helix.

The goal of this paper is an interpretation of the chiral discrimination between an extended chiral helicoidal system and an amino acid molecule. The helix schematizes, in a very simple way, the helicoidal polymer phase or the chiral cavity whereas the analyte is represented by a molecule with a tetrahedrally substituted carbon atom. This model is obviously far from the reality in regard

to the complexity of the enantiomeric selectivity experiments since, first, the chiral systems are highly idealized and, second, the influence of the solvant is disregarded. But it is expected to give basic informations on the relative contribution of the various types of interactions leading to chiral recognition of *L* and *D* amino acids by helicoidal or cavity phases.

The model

We consider an helix with different radii ρ and pitches B, smaller or larger than the chiral analyte molecule.

This helix is formed by the spatial arrangement of glucose rings with a monomer length equal to L [3]. This monomer is formed by polarizable centers, hidrogen-bond centers and electrical dipole moments.

The common α-amino acid molecule R-CH (NH_2) CO_2H can be schematized by a tetrahedrally substituted carbon atom. For alanine, which appears as the simplest chiral amino acid, one has $R \equiv CH_3$ and this molecule is described as a polarizable, dipolar zwitterion.

The amino acid chirality is described by the relative locations of two of their groups; the laevogyre and dextrogyre enantiomers are obtained by permuting the positions of this groups in the moleculer [2, 11].

The interaction potential

The interaction potential V between the helix and the molecule is written as:

$$V = V_{ach} + V_{ch} \tag{1}$$

where the two contributions characterize achiral and chiral interactions, respectively.

1. Achiral terms

The achiral terms appear as a combination of hydrogen bonding V_H, ionic V_I, dipolar V_D and induction V_{P1} contributions, as:

$$V_{ach} = V_H + V_I + V_D + V_{P1} \tag{2}$$

A Lippincott-Schroeder-type potential is used to describe the hydrogen bond term V_H. This potential, although achiral, is highly selective in position and direction and it is expected to freeze the center of mass and the orientation of the molecule.

The ionic potential V_I generally occurs due to the ionic character of the amino acid; it describes the interaction between the molecule ions and the helix dipoles.

The dipolar potential V_D characterizes the interaction between the helix and molecule dipole moments.

These two contributions V_I and V_D are achiral although the helix dipole moments have a chiral structure. But the charge and dipole distributions in the model amino acid are not chiral since chirality would require three ionic charges at least and dipoles located in different planes (the directions of these dipoles

must not intersect at a single point). The hypothesis of dipoles collinear with the four bonds rules out this condition.

The latter term in eq. (1), V_{P1} characterizes the polarization of the helix by the ions and dipoles of the amino acid molecule.

2. *Chiral terms*

The chiral interactions are represented by two potentials, the Lennard-Jones terms V_{LJ} and the induction one V_{P2}, as:

$$V_{ch} + V_{LJ} + V_{P2} \tag{3}$$

The second chiral term corresponds to the polarization of the amino acid molecule by the dipoles of the helix.

3. *Equilibrium energy and chirality*

The interaction energy V (eq. (1)) depends on the position (X, Y, Z) of the center of gravity of the amino acid molecule and on the orientation (φ, ϕ, ψ) of this molecule with respect to the helix. The equilibrium configuration for the two interacting systems at $T = 0$ is obtained for a vanishing force, i.e. by solving the system of equations:

$$F_u = -\nabla_u V(\{u\}) = 0 \tag{4}$$

where $\{u\} \equiv \{X, Y, Z, \varphi, \phi, \psi\}$. The values of u which correspond to this equilibrium are noted as u_L or u_D according to the enantiomer of the amino acid molecule. Due to the chiral potential V_{ch}, these values u_L and u_D are different and thus introduce a differential contribution in the achiral term since $V_{ach}(u_L) \neq V_{ach}(u_D)$, in general.

The discriminatory ratio Δ_v is defined as:

$$\Delta_v = \frac{|V(u_L) - V(u_D)|}{|1/2\,[V(u_L) + V(u_D)]|} \tag{5}$$

Results

Specific interactions such as hydrogen bondings are mainly local; they do not significantly depend on the helix characteristics but are rather defined by the possible bridges in the glucose ring.

When all the other interactions are switched off, the value of the hydrogen bond interaction is close to -1.2 eV for the bridges between the glucose and the amino acid. Variations of about ± 0.2 eV around this value take into account the small changes of the equilibrium distance which would be due to the influence of the other interactions.[3] However, when all the potential contributions are considered, they tend to decrease by a factor 2 the interaction energy at the location of the H bridges because the hydrogen bond geometry does not correspond to a stable configuration for the electrostatic and chiral contributions. The main feature of the hydrogen bond interactions is the occurrence of

sharp peaks in the potential energy surface [6] due to the high degree of selectivity of this type of interaction (Fig. 1).

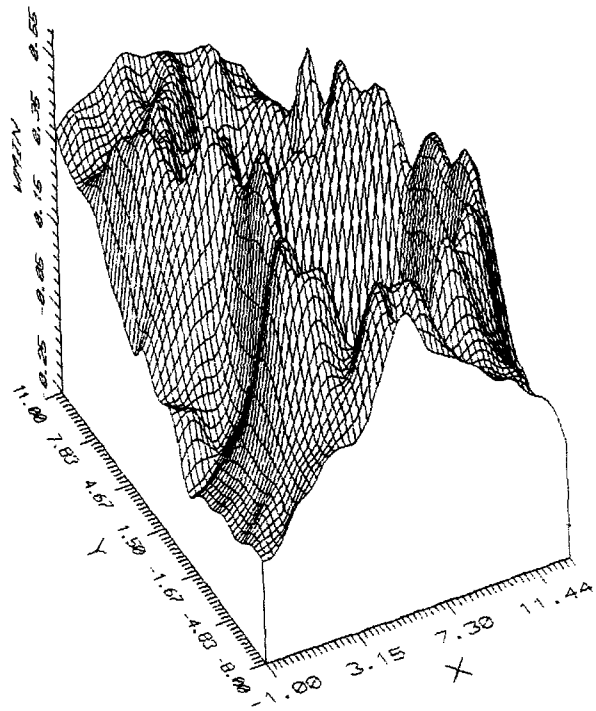

Fig. 1. Potential surfaces $V_{\min}(x, y) \equiv -V$ vs. the location (x, y) of the central carbon atom of the amino acid molecule. Distances in Å and energy in eV

The electrostatic interactions are sensitive to the helicity of the chiral phase since they are long range contributions. While they vary like the second and third inverse powers of the intermolecular distance and therefore do not mainly contribute to the determination of the energy minimum location, their angular dependence is rather large. The electrostatic terms can contribute by 30 to 50% to the total potential.

The potential V_{ach} acts as a chiral revealer by first freezing the degrees of freedom of the amino acid molecule and second by providing a differential contribution to the equilibrium energy since the equilibrium coordinates u_L and u_D are different.

At last, the Lennard-Jones V_{LJ} and induction V_{P2} terms are closely connected to the spatial distribution of the atoms in the two systems. Special emphasis is brought to the determination of their influence on the total interaction according to the helix structure (Fig. 2).

The equilibrium distances between the amino acid molecule and the helix are only modified by a small amount with respect to those determined with a Lennard-Jones potential. The equilibrium energy values vary between -0.50 eV and -0.85 eV, and have a similar magnitude than the hydrogen bond interactions.

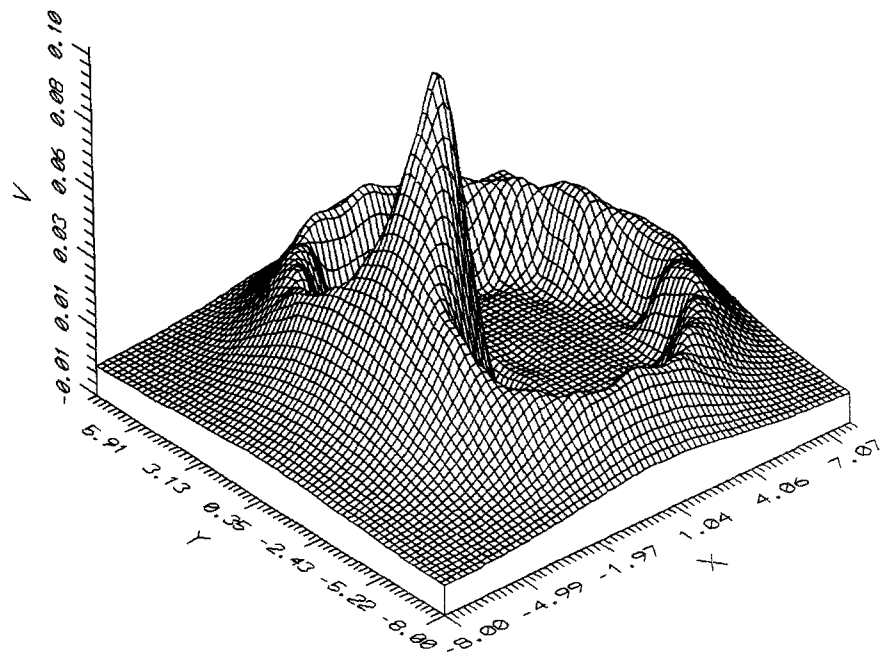

Fig. 2. Potential energy surface for the chiral contribution (here $V = -V_{ch}$) vs. the position (X, Y) of the central carbon atom of the amino acid molecule with $\rho = 3$ Å and $B = 1.5$ Å rad^{-1}. Note that the repulsive parts of the surface have been arbitrarily taken to be zero, for clarity

The energy differences for the two diastereoisomers "helix-*L* amino acid" and "helix-*D* amino acid" vary from $5\ 10^{-4}$ eV to $2\ 10^{-2}$ eV for the chiral contribution. On the contrary, the energy differences for the achiral contribution remain larger, between 10^{-2} and $5\ 10^{-2}$ eV, and they have not necessarily the same sign as the chiral term.

The discriminatory ratio Δ_V is maximum when the amino acid is close to the helix axis since it reaches about 6%, or when the amino acid penetrates easily the helix cavity ($\Delta_V \simeq 8\%$). When the helix pitch increases, the chiral ratio Δ_V tends to decrease, but it remains larger than 1% in all cases.

The discriminatory ratios Δ_{VLJ} and Δ_{VP2} are significantly different according to each case. This shows that each contribution acts very differently depending on the situations and there is no general rule for the chirality recognition due to subtle antogonistic effects. Indeed, the discriminatory power of the induction term V_{P2} is clearly very large but its contribution to the total energy remains weak when compared to the Lennard Jones term with a much smaller discriminatory power but a larger contribution to V.

Conclusion

The goal of the present study was an estimate of the various contributions to the interaction potentials involved in a highly modelized system of chiral recognition. The chiral separator was described by an helix with varying pitch and radius and the analyte molecule by an amino acid zwitterion.

Three species of interactions have been identified. Hydrogen bond interactions are nearly unsensitive to the geometry of the interacting systems and they are achiral and mainly local. They obviously provide a fundamental contribution to the interaction potential and to the discriminatory ratio as they freeze the position and orientation of the amino acid molecule. When the glucose rings are arranged along an helix or a circular cavity, the density of hydrogen bridges increases and favors the analyte molecule trapping. On the contrary, the electrostatic interactions strongly depend on the conformation of the separator and of the analyte. They are not generally chiral, as shown here, but they freeze the amino acid orientation and reveal chirality. Their magnitude, although smaller than that of hydrogen bond, is similar to the magnitude of the third species of interations. These third species (Lennard-Jones and induction terms) are chiral and they crucially depend on the mutual geometry of the two interacting systems, since they characterize the spatial distribution of atomic matter. The chiral discriminatory ratio increases when the analyte molecule is located inside the cavity formed by the helix and is maximum for similar sizes of the cavity and of the analyte. This latter feature is crucial for optimal chiral recognition, as empirically seen in chiral phase chromatography.

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