Pergamon

Tetrahedron Letters, Vol. 37, No. 15, pp. 2581-2584, 1996

0040-4039/96 $15.00 + 0.00

S0040-4039(96)00375-9

Role of van der Waals Forces in Enantioselective Processes

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Abstract: Calculation of chiral recognition energy based on the simple model and van der Waals potential with usual van der Waals parameters indicated that the chiral recognition energy is of the order of 0.1 kcal/mol when the molecules are far away (in the attractive region) while it is of the order of 10 kcal/mol when the molecules are close to each other (in the repulsive region). Thus, this study indicates that the external forces bringing two molecules close to each other lead to quite high chiral recognition based on van der Waals forces. Copyright © 1996 Elsevier Science Ltd

Enantioselective molecular recognition is a key elementary process for asymmetric synthesis and enantiomer separation of biologically important molecules. In many examples of asymmetric synthesis, steric repulsion between substrate and catalyst is suggested to be one of the major factors of determining the chiral selectivity.[1-2] Such van der Waals interaction is universal and consists of two terms, attractive term and repulsive term. One of the goals of this study is to clarify the role that these two terms play in chiral molecular recognition.

To deal with this issue, we constructed a simple model consisting of two molecules, ABC, A'B'C', each of which has only three atoms. Angles ABC, BCA, A'B'C', and B'C'A' are all set to 60° and the intramolecular atomic distances AB and A'B' are fixed to 2 Å. Then, the geometry of the system is determined by three parameters, θ_1, θ_2, and $R_{AA'}$ (Fig. 1). We minimized the potential energy of the system for a fixed $R_{AA'}$ by optimizing θ_1 and θ_2. The values of θ_1 and θ_2 were varied between 0° and 60° in 0.25° steps and the geometry giving the minimum potential was searched by numerical calculations. As a pairwise potential we employed the Lennard-Jones type potential: U_{AB} (kcal/mol) = $P \exp(-12.5r^*) - Q/r^{*6}$, where $P = 2.9 \times 10^5 (\varepsilon_A\varepsilon_B)^{0.5}$, $Q = 2.25 \times (\varepsilon_A\varepsilon_B)^{0.5}$, $r^* = 2r / (r_A + r_B)$, ε_A and ε_B are the van der Waals energy parameters, and r_A and r_B are van der Waals radii. The potential energy of the system was assumed to be $U_{BB'} + U_{BC'} + U_{CB'} + U_{CC'}$.

The representative result is shown in Figure 2. When the atom A and atom A' are far away, the potential energy of configuration **1**, U_1, is almost the same as that of the diastereomeric configuration **2**, U_2. As the two molecules come closer, the U_1 value and the U_2 value become different. There was one minimum for U_1 at $R_{AA'}$ = 4.7 Å, at which distance two molecules are in van der Waals contact with each other. The minimum for U_2 appeared at a longer intermolecular distance of $R_{AA'}$ = 4.9 Å. The potential energy increased rapidly when the AA' distance is shorter than 4.5 Å due to steric repulsion.

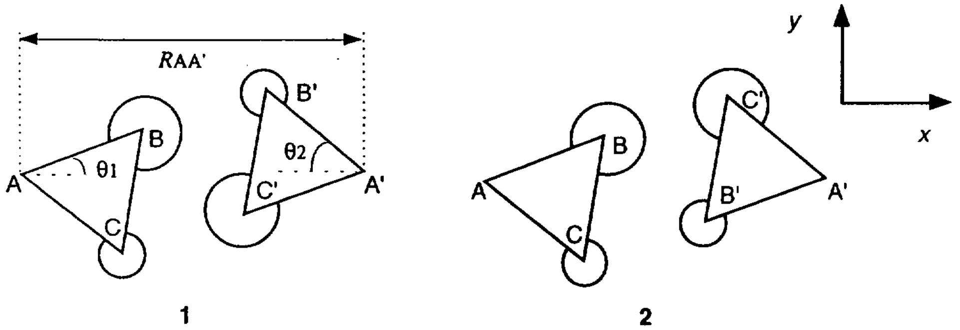


Figure 1. Model for chiral recognition. Centers of Lennard-Jones potential were placed at points B, B', C, and C'. The total potential energy between the two molecules was optimized for two parameters, θ_1 and θ_2, for each distance AA', where θ_1 and θ_2 are angles between x-axis and vector AB and vector A'B', respectively. The minimum potential energies for configuration **1** and configuration **2** are denoted as U_1 and U_2, respectively. The difference in U_1 and U_2, ΔU, is the chiral recognition energy for the complexation between molecule ABC and molecule A'B'C'.

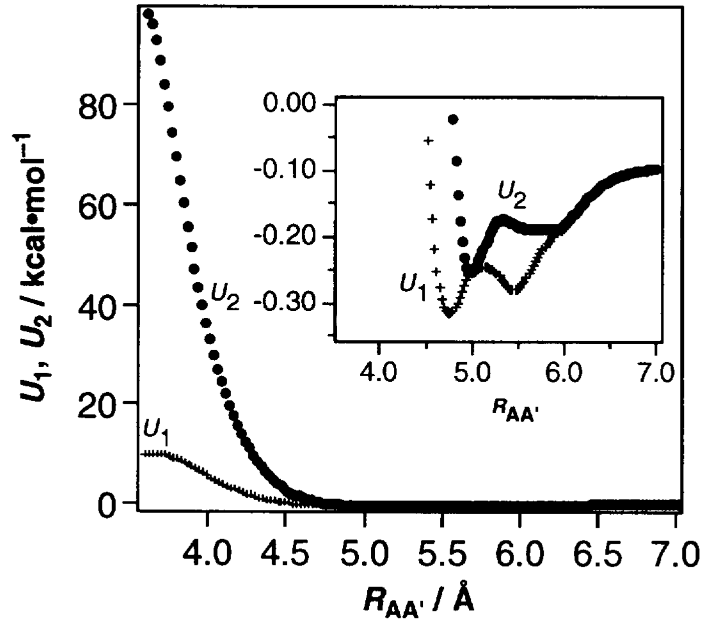


Figure 2. Plot of potential energy for optimized configuration **1** and **2** as a function of distance AA' ($R_{AA'}$). U_1 and U_2 were calculated by assuming $R_{AB} = R_{A'B'}$ = 2 Å, $r_B = r_{C'}$ = 1.5 Å, $r_C = r_{B'}$ = 0.5 Å, and $\varepsilon_B = \varepsilon_C = \varepsilon_{B'} = \varepsilon_{C'}$ = 0.08 kcal/mol.

Chiral Recognition at Equilibrium Configuration. The energy difference between the U_1 minimum and the U_2 minimum can be taken as the chiral recognition energy ΔU. The values of ΔU are dependent on the van der Waals parameters of atoms B, B', C, C' and are shown in Table 1. As the ratio of van der Waals radii and the difference in the van der Waals energy parameters (ε) of atom B, B', C, C' become large, the value of ΔU increased almost linearly. However, the magnitude of ΔU would not exceed 0.1 kcal/mol in this system.[3]

Chiral Recognition at Configuration Fixed with External Forces. If any external forces restrict the AA' distance to a certain fixed value, the difference in U_1 and U_2 at each distance of AA' ($\Delta U(R_{AA'})$) is an important measure of chiral recognition energy. For example, to reach the transition state of a reaction, the distance between atom A and atom A' falls in a small range. For such a case consideration of the values of $\Delta U(R_{AA'})$ in a repulsive region (a small AA' distance) becomes important.

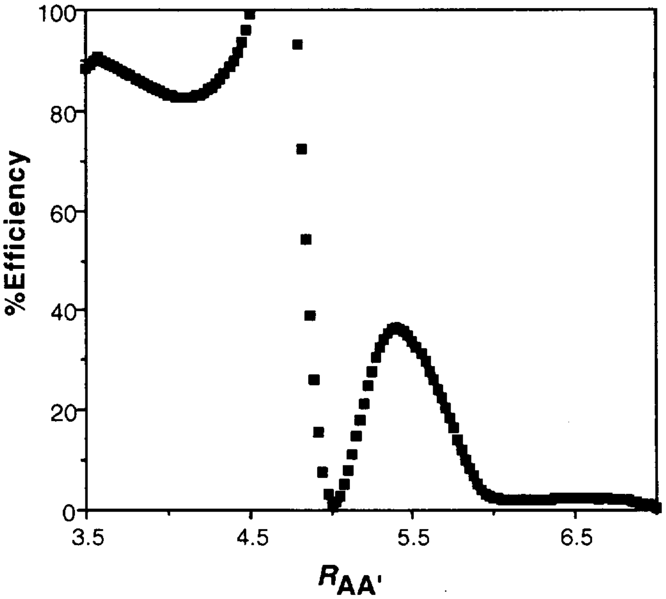
Figure 2 indicates that, at a distance of AA' longer than 5.0 Å, the chiral recognition energy, $\Delta U(R_{AA'})$, was of the order of or smaller than 0.1 kcal/mol. The value of $\Delta U(R_{AA'})$ becomes much larger at an AA' distance shorter than 4.5 Å, being of the order of 10 kcal/mol. Thus, in the repulsive region where two molecules are in van der Waals contact or closer, the chiral recognition energy can be significant. To estimate the fraction of energy used for chiral recognition out of the total binding energy, we define the efficiency of chiral recognition, *%e*, as shown in equation (1).

$$\%e = |(U_1 - U_2) / \max(|U_1|, |U_2|)| \times 100 \qquad (1)$$

In Figure 3 is shown a plot of *%e* against the AA' distance. For a long intermolecular distance, the chiral recognition is inefficient. At $R_{AA'} = 5.4$ Å, the *%e* value shows a peak, and then becomes zero at 5 Å. A smaller distance of $R_{AA'}$ than 4.5 Å leads to a very efficient chiral recognition (*%e* > 80%). At $R_{AA'}$ = 4.75 Å, two molecules of **1** are in van der Waals contact with a face-to-face configuration.

Table 1. Equilibrium Chiral Recognition Energy (ΔU) Calculated for Various van der Waals Energy Parameters (ε) and van der Waals Radii (r)

ε_B, kcal/mol	ε_C, kcal/mol	r_B, Å	r_C, Å	ΔU, kcal/mol
0.04	0.08	1.5	1.5	–0.013
0.04	0.12	1.5	1.5	–0.023
0.04	0.2	1.5	1.5	–0.040
0.04	0.4	1.5	1.5	–0.069
0.04	0.6	1.5	1.5	–0.092
0.08	0.08	0.5	1.5	–0.021
0.08	0.08	0.6	1.4	–0.016
0.08	0.08	0.7	1.3	–0.011
0.08	0.08	0.9	1.1	–0.003



Selected values of θ_1 and θ_2 for each $R_{AA'}$ distance

	1		2	
$R_{AA'}$/Å	θ_1	θ_2	θ_1	θ_2
4.75	51.5	8.8	49.0	60.0
5.00	48.0	12.0	58.5	60.0
5.45	32.8	27.3	32.8	60.0

Figure 3. Plot of efficiency of chiral recognition (*%e*) against AA' distance (left), and values of θ_1 and θ_2 (right).

This work demonstrates that van der Waals forces themselves lead to 0.1 kcal/mol of chiral recognition energy, while restriction of configuration by other external forces can enhance the chiral recognition energy to the order of 10 kcal/mol, in which configuration the repulsive van der Waals forces are dominant.

REFERENCES and NOTES

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3. The chiral recognition energy of 0.1 kcal/mol amounts to 8.3% ee at 300 K estimated from %ee = tanh ($-\Delta G°/2RT$) × 100(%) if the entropy term is neglected. Similarly, that of 4 kcal/mol amounts to 99.7 %ee.

(***Received in Japan*** **27** ***December*** **1995;** ***revised*** **15** ***February*** **1996;** ***accepted*** **23** ***February*** **1996)**