D–L Conversion Pathways between Optical Isomers of Alanine: Applications of the Scaled Hypersphere Search Method to Explore Unknown Reaction Routes in a Chiral System

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D–L conversion pathways of α-alanine have been discovered by theoretical search of potential energy surfaces at the level of B3LYP/6-311++G(d,p). No direct conversion channel via only one transition state could be found between D and L optical isomers of alanine. It is demonstrated that there are four types of conversion channels in chiral amino acids. The interconversion of four functional groups (H, CH_3, NH_2, and COOH) around the asymmetric carbon atom can occur as rotation of a single-bonded pair of two groups involving either NH_2 or COOH together with H or CH_3.

Chirality is an important property of molecules especially in stereochemistry and biochemistry.[1–3] Selective preparation of pure enantiomers with chirality has been developed by the use of a specific catalysist to its chiral precursor.[2] Chiral molecules can also be produced by photoreactions of racemic mixtures by irradiation of a right or left circularly polarized laser, though the resultant yield of enantiomer excess is very low.[3] Recently, quantum control of molecular chirality by the use of the coherent nature of lasers has been proposed theoretically.[4]

In connection with life science, chirality of amino acids is of great significance. There are fundamental questions, why one particular type of optical isomers of amino acids appears in life bodies, why their chirality is maintained, and how the optical isomers can be converted each other. The last problems of conversion reactions between optical isomers of amino acids have not been elucidated hitherto, although quantum chemical calculations may be applied to this problem in principle.

Reaction route mapping can be made theoretically by searching for equilibriums (EQ) and transition states (TS) on potential energy surfaces (PES) obtained by quantum chemical calculations. However, global search of reaction routes including discovery of unknown reaction pathways in a systematic way has been a very difficult problem, because of too heavy computational demands due to almost infinite procedures in the multidimensional PES.[5,6]

Recently, we developed a new technique, the scaled hypersphere search (SHS) method, which makes it possible to explore unknown reaction pathways on PES one-after-another in an automatic way within finite procedues.[7,8] The SHS method enables us to follow reaction pathways from EQ to neighboring TS, noting that the potential energy along a reaction path becomes lower than the respective harmonic potential. The SHS method detects such anharmonic downward distortions of PES as energy minima on a hypersurface which would have a constant energy if the potentials are harmonic. The SHS method can be used for global mapping of reaction routes by finding out all reaction pathways leading to anharmonic downward distortions.

In this study, intramolecular D–L conversion pathways of α-alanine have been discovered by the application of the SHS method to exploring potential energy surfaces at the level of B3LYP/6-311++G(d,p). Potential energies in the singlet ground state were obtained by the quantum chemical HF/6-31G level of calculations based on a Gaussian03 program package.[9] Geometries and energies for all EQ and TS were further refined and confirmed at B3LYP/6-311++G(d,p) level of calculations. At each refined EQ or TS, normal coordinate calculations were made to make zero-point-energy (ZPE) corrections. From each TS, downhill procedures toward both sides were made to determine the minimum energy path or the intrinsic reaction coordinate (IRC)[10] by a conventional downhill technique of the steepest descent method based on the second-order algorithm using gradient and Hessian.[11]

Figure 1 demonstrates D–L conversion pathways between optical isomers of alanine. Starting from one of the most stable isomers with point chirality, reaction pathways leading to neighboring TS were searched systematically from its EQ. No achiral TS directly connected with the D or L form could be found. This indicates that there is no direct conversion channel via only one TS exists between D and L isomers of alanine. This finding is of great importance to understand the stability of a particular type of chirality of amino acids in life bodies. As can be seen in Figure 1, four conversion channels, (A), (B), (C), and (D), were discovered between D and L alanine molecules.

Channel (A) includes two TS with point chirality and one achiral intermediate state. Channel (B) is a pathway via a chiral TS into an intermediate with helical chirality, which is then transformed to another intermediate with the opposite helical chirality via one of two equivalent TS with helical chirality. Channels (C) and (D) surmount a chiral TS to descend to an intermediate with axial chirality, which is then transformed to its counterpart with the opposite chirality via an achiral TS.

Since the first TS in every channel has a high barrier larger than 180 kJ mol^{-1}, an alanine molecule is kinetically stable enough to keep its own chirality under thermally mild conditions. At a very high temperature, the preference of D–L conversion routes is expected to become (C) > (D) > (A) > (B) from the magnitudes of the barrier heights of respective TS.

Intermediates in (A) and (B) are ionic species of $(RNH_2)^+(R'C)^-(COOH)$ with R,R′ = H or CH_3, whereas intermediates in (C) and (D) are covalent species of $RC(OH)_2$–CR′=NH with one imino and two hydroxy groups.

The interconversion of four functional groups (W, X, Y, and Z) around the asymmetric carbon atom (C*) can be summarized by Scheme 1.

With fixing W and X, a combination of Y and Z once generates an intermediate species with a single-bonded structure of C–(YZ) which then rotates to its counterpart to yield the other optical isomer with the opposite chirality. The direct rotation of

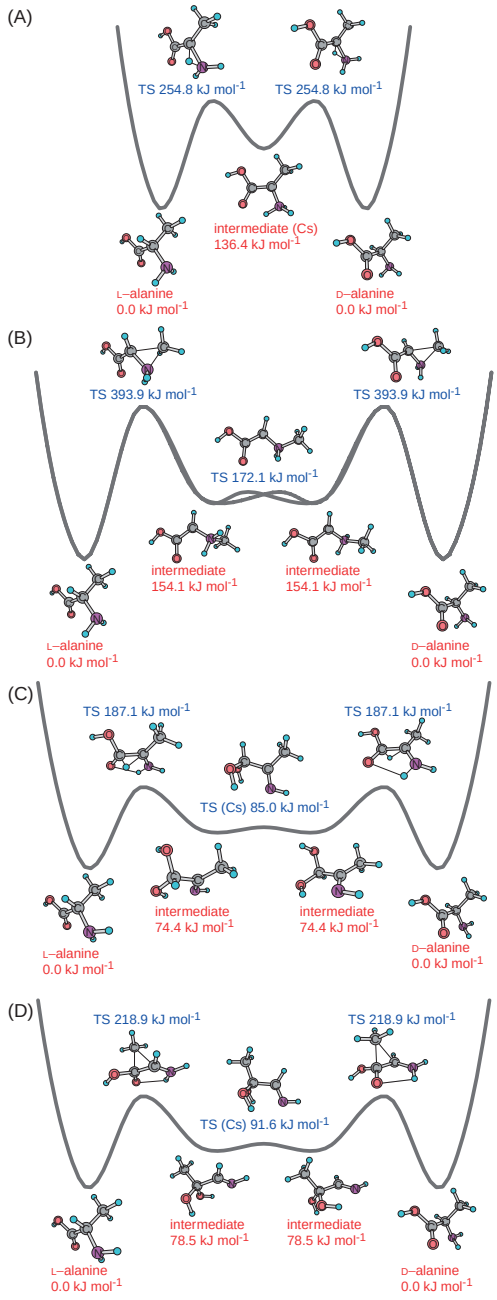
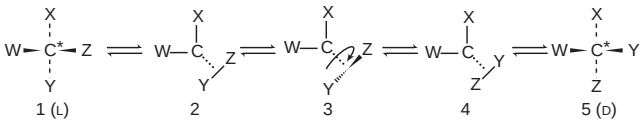


Figure 1. D–L Conversion pathways between optical isomers of alanine. For each conversion route, only the lowest energy pathway is shown. Except for the mid point in each route, left and right structures at a pair of mirrorimage isomers are counterparts with opposite chirality. (A) Conversion channel via an achiral intermediate. (B) Conversion channel via intermediates with helical chirality. (C) and (D) Conversion channels via intermediates with axial chirality.

Y–C–Z with respect to W–C–X is forbidden because of the very strong constraint of the sp^3 hybrid. Among six possible combinations interchanging a couple of functional groups around the asymmetric carbon atom of alanine, (H, NH_2), (CH_3, NH_2), (H, COOH), and (CH_3, COOH) are allowed for the D–L conversion channels of (A), (B), (C), and (D), respectively, while the remaining combinations of (H, CH_3) and (NH_2, COOH) are forbidden for D–L conversion; (H, CH_3) results in dissociation into



Scheme 1.

CH_4, and (NH_2, COOH) only returns to the same form via an sp^3 form with a lone pair. It follows that the D–L interconversion in the amino acid molecule can only occur by the rotation of the single-bonded pair of either NH_2 or COOH with an alkyl group R = H and CH_3.

The present results for alanine based on the SHS method provide valuable information to perform quantum control by coherent laser excitation.[4] Reaction route mapping for larger systems will provide new reaction pathways for chiral systems in stereochemistry and biochemistry.[2]

The present study has been made by a use of a conventional laboratory-size computer of 3 G Flops (floating point number operations), and its application to a thirteen atomic system of alanine molecule yielded interesting results, as shown above. If one may use an excellent computing system of 1–100 T Flops (http://www.top500.org), unknown reaction routes of much larger systems as well as many other interesting systems can be studied by the SHS method.

The SHS method is concluded to be a powerful method to explore unknown reaction routes one-after-another in a systematic way within finite computational procedures. In previous studies, the SHS method has been used to discover global isomerization pathways for CH_3CN[12] and HC_3N,[13] isomerization pathways of alanine-dipeptide[14] as well as new synthetic (decomposition) pathways of the simplest amino acid molecule of glycine (H_2NCH_2COOH).[15,16] In the present study, D–L conversion pathways of α-alanine ($H_2NCH(CH_3)COOH$) could be discovered as minimum energy pathways on PES by use of the SHS method.

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