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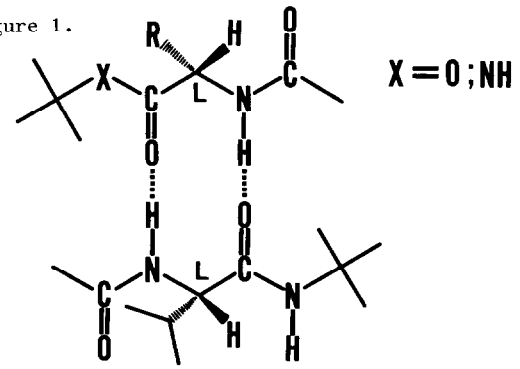
CHIRAL RECOGNITION OF AMINO ACID ENANTIOMERS APPLYING ASSOCIATION MODELS OF AMINO ACID DERIVATIVES FORMING INTERMOLECULAR HYDROGEN BONDS

Akira Dobashi and Shoji Hara*
Tokyo College of Pharmacy, Horinouchi, Hachioji, Tokyo 192-03, Japan

ABSTRACT: Chelate-like association of amino acid derivatives made up by intermolecular NH••O=C hydrogen bonds can function as chiroselective complexation for resolution of D- and L-amino acid derivatives.

Recognition of molecular chiralities is made on the basis of the different affinities of chiral molecules toward enantiomers to be resolved[1]. We report in this paper that the association modes of amino acid derivatives consisting of intermolecular NH•• O=C hydrogen bonds[2] can function to bring about chiroselective complexation in the resolution of the D and L enantiomers of amino acid derivatives. Chiral N-acetyl-L-valine tert-butylamide was used as a chiral resolving agent in liquid-solid chromatography. This resolving agent can offer hydrogen bonding sites through two amide units to the amino acid derivatives to be resolved. These derivatives have two types of structure: N-acetylamino tert-butyl ester and N-acetylamino acid tert-butylamide. Of the two, the latter had the same derivatizations of N- and C-terminal groups as those of the resolving agent. Diastereomeric associations resulting between the chiral resolving agent and the enantiomers bring about only slight conformational differences even though the associated structures are assumed to have a maximum number of bidentate NH•• O=C hydrogen bonds. Thus, it is difficult to determine what factors impart additional stability to one of the associated enantiomers. However, in spite of the weak association energy of the hydrogen bondings, these diastereomeric associations were found to have enough difference in stability to permit resolution of the enantiomers of the amino acid derivatives with the aid of high efficient chromatographic technology.

Figure 1.



Resolution of amino acid enantiomers was accomplished on a silica gel column using a chiral mobile phase containing N-acetyl-L-valine tert-butylamide[3]. It is reasonable to expect that the chiral resolving agent interacts with the D and L enantiomers of the solute to afford diastereomeric association in equilibrium as these chemical species pass through the column. Baseline separations in chromatography were observed for all enantiomers, affording a separation factor in the range of 1.13-1.28. Some of the results are presented in Table I. The separation factors cover a range of $-\Delta(\Delta G^{\circ})$ values from 76 to 154 cal/mol, reflecting the difference in the free energy of the associated enantiomers[4]. Though these values are fairly small compared to those given by the other specific complexations such as host-guest[5] and metal chelate

Table I Chiral Recognition by Chiral Resolving Agent of N-Acetyl-L-Valine tert-Butylamide[a]

solute	mobile phase ratio of $CHCl_3$ in n-hexane	capacity factor[b] k'_1	capacity factor[b] k'_2	separation factor (α)[c]	$-\Delta(\Delta G^\circ)$ cal/mol[d]
N-Ac-Trp(Bu^t)-OBu^t [e]	40/60	2.93	3.65	1.25	139
N-Ac-Cys(Bzl)-OBu^t	40/60	3.12	3.75	1.20	113
N-Ac-Phegly-OBu^t	40/60	3.36	4.09	1.22	124
N-Ac-Phe-OBu^t	40/60	3.51	4.49	1.28	154
N-Ac-Phe-$NHBu^t$	80/20	8.92	10.11	1.13	76
N-Ac-Tyr(Ac)-OBu^t [e]	50/50	10.29	12.09	1.17	98

a) The mobile phase solvent was chloroform-n-hexane containing 14.02 mM of the chiral resolving agent. The column and other operating details are presented in ref. 3. b) The capacity factor (k') is the net retention time relative to the dead time of the column: k' = (the retention time of the enantiomer - the dead time)/(the dead time). c) Separation factor (α) reflects the difference in stability between the associated enantiomers: $\alpha = k'_2/k'_1$. d) see ref. 4. e) The order of the emergence was such that the D enantiomer was followed by the L enantiomer.

complexations[6], the system using the hydrogen-bond association permitted weak but sufficient chiral recognitions. The relative orientation of the side chains attached to the asymmetric carbons in two amino acid derivatives assembled together determines the difference in stability of the corresponding diastereomeric association when dimer models, in which bidentate NH•• O=C hydrogen bonds are formed between the resolving agent and the solute, are assumed for the hydrogen-bond association as illustrated in Figure 1. The preliminary results provide a useful means for investigating the enantioselectivity of hydrogen-bond association frequently involved in enzymatic chiral recognition in spite of facile and flexible interactions. Our method should also make possible the design of a novel chiral recognition system which can use various kinds of chiral molecules containing proton-releasing or proton-accepting groups.

REFERENCES AND NOTES

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2) Prior NMR studies have shown that amino acid derivatives such as N-acetylamino esters and N-acetylamino acid amides exhibit chelate-like associations in which bidentate NH•• O=C hydrogen bonds are formed between adjacent molecules: T. Asakura, M. Kamio, and A. Nishioka, Biopolymers, 18, 467 (1979); reference cited therein.
3) The packing was a silica gel (E. Merck, LiChrosorb Si 60 (5 μm)), with a column of 25 x 0.4 (i.d.) cm. The chromatography was made under the following conditions: flow rate, 1 ml/min; column temperature, 40°C. The appearance of the enantiomers in the column eluate was detected by ultraviolet absorption at a wavelength of 265 nm.
4) The $-\Delta(\Delta G^\circ)$ value was calculated by the equation, $-\Delta(\Delta G^\circ) = RT\ln\alpha$, under ideal conditions. Even though chromatographic conditions are generally not ideal, these values obtained allow us to conventionally discuss the results of chromatographic separation in terms of free energy change.
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