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Molecular Chiral Recognition In Supercritical Solvents

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Abstract: The intensity of molecular chiral interactions resulting in differences between physical and chemical properties of diastereomeric molecules is solvent dependent. This difference makes it possible to separate the enantiomers of a given substance by using chiral agents. A solvent of supercritical state was involved to study its influence on molecular chiral recognition. It was observed that the differences between the diastereomers in supercritical CO_2 are so big compared to traditional solvents that a novel, more efficient method for optical resolution can be developed, employing a variety of resolution agents in a much wider range than it was previously assumed.

The oldest example of molecular chiral recognition, described by Pasteur,[1] is the separation of enantiomers based on diastereomeric salt formation and fractionated crystallization. The principle of the enantiomeric differentiation is that one of the salts formed with a chiral reagent is less soluble than the other , and thus precipitates from the solution. This enrichment of one of the enantiomers makes the optical resolution possible. In this way a filtration furnishes a solid salt enriched with one of the enantiomers, and a mother liquor containing predominantly the other enantiomer. Even nowadays, particularly in industrial processes, the separation of enantiomers of racemic acids and bases is based on this molecular chiral recognition. The less soluble, i.e. the more stable of these diastereomers formed in this way crystallizes out even if the chiral reagent in-the better soluble salt is replaced by an achiral reagent[2] of similar chemical character, or eventually eliminated[3], or substituted by a solvent.[4] In this case, a mixture enriched with the more stable diastereomer can be isolated by filtration from the solution of the achiral salt of the enantiomeric mixture or the free enantiomers.

This latter method can also be modified in a way that the crystallization of the diastereomeric salt is not necessary. It can even be realized without solvent. The enantiomeric recognition and differentiating effect of the chiral reagent is operating even in the case when the mixtures of the diastereomer and the enantiomers are separated by thermal treatment by condensing the vapours evolved from the mixture.[5,6]
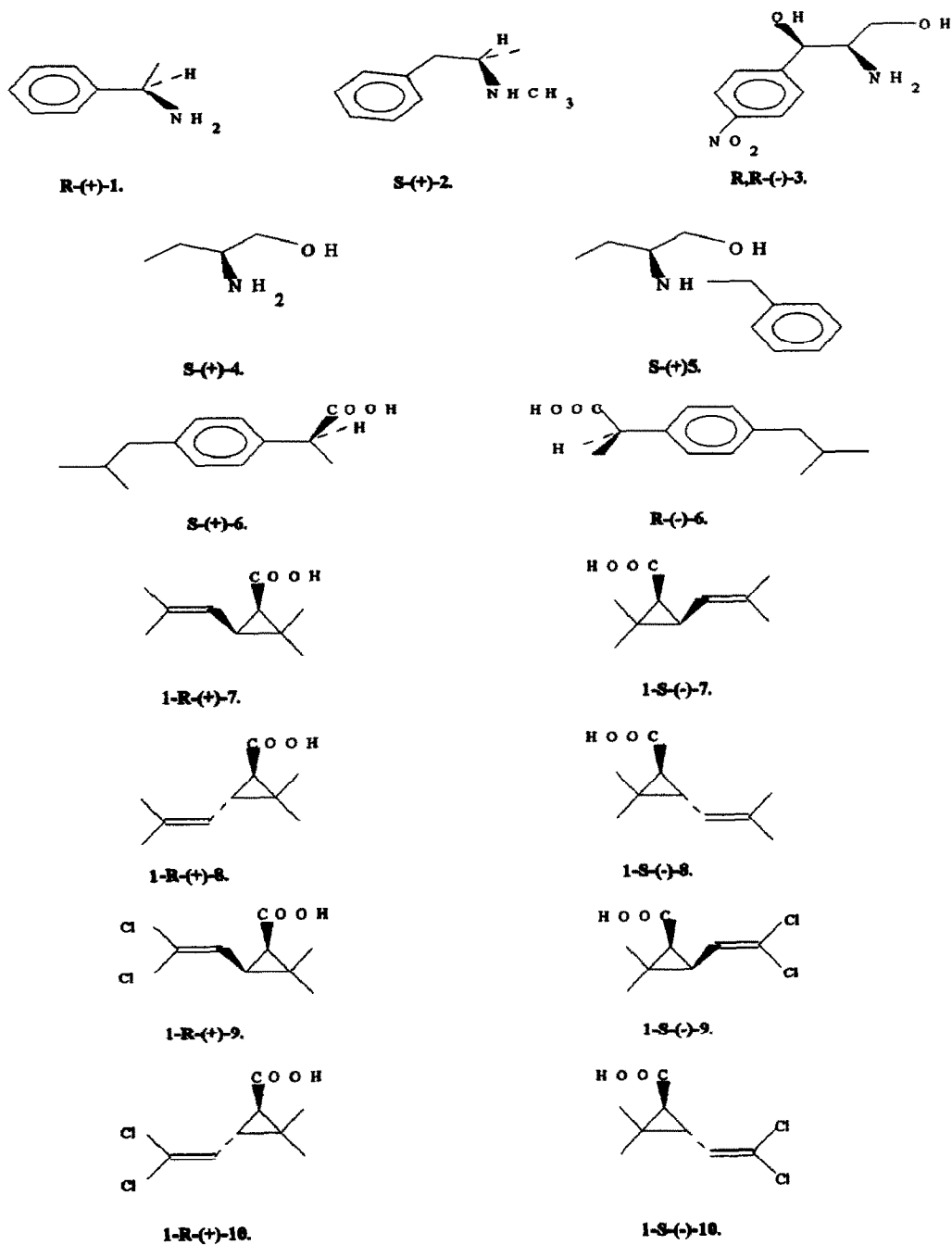
These findings concluded that the role of the molecular chiral recognition is very important; it can exceed that of the diastereomers. It is well known that the solubility of substances in solvents of supercritical state changes. The supercritical gases, however, can be easily eliminated from their solutes[7,8].

As good enantiomeric separation has been achieved by supercritical fluid extraction by employing chiral stationary phases[9], we anticipated that the separation of enantiomers from a mixture of enantiomers and diastereomers is possible on the basis of chiral molecular recognition. The optical purity achieved by the separation can be a characteristic parameter of the extent of molecular chiral differentiation.

We investigated the molecular chiral recognition by preparing mixtures of racemic acids (6-10) with various chiral bases (1-5) in 1:0.5 molar ratio (Table 1.). A solid, porous supporting material, "impregnated" with these mixtures, was extracted with supercritical solvent (CO_2). The extracts were free enantiomeric

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mixtures, whereas the residues were the corresponding mixture of diastereomeric salts. We have separated the enantiomeric mixtures from those of the diastereomeric salts.

Table 1.
Resolution agents, Racemic compounds

R-(+)-1.

S-(+)-2.

R,R-(-)-3.

S-(+)-4.

S-(+)5.

S-(+)-6.

R-(-)-6.

1-R-(+)-7.

1-S-(-)-7.

1-R-(+)-8.

1-S-(-)-8.

1-R-(+)-9.

1-S-(-)-9.

1-R-(+)-10.

1-S-(-)-10.

The optical purity values in percents and the configuration of the major enantiomeric components are collected in the Table 2. It can be concluded that the molecular chiral recognition in a supercritical solvent is much more sensitive and has a wider range of application than the known methods employed for the separation of enantiomeric mixtures. This is also supported by the fact that in the majority of cases the extent of chiral recognition is not sufficient to guarantee the separation of the mixture. The chiral agent 3 is capable of differentiating the enantiomers of all the five racemic compounds, which has been described[8] only for the racemic compound 6. The effect of the chiral reagent 1 was nearly the same: it proved to be suitable for differentiation in four cases, whereas earlier this has been exclusively known only for the separation of the enantiomers of 6.

Table 2. Optical purity data

| Racemic compounds | Resolving agent | | | | |
	1.	2.	3.	4.	5.
6.	R-(-)-6.-1. 35,0% S-(+)-6. 41,7%	R-(-)-6.-2. <0,5% S-(+)-6. 1,5%	R-(-)-6. 11,0% S-(+)-6.-3. 14,0%	—	—
7.	R-(+)-7.-1. 2,3% S-(-)-7. <0,5%	—	R-(+)-7. 2,6% S-(-)-7.-3. 1,8%	R-(+)-7. 4,0% S-(-)-7.-4. 4,4%	R-(+)-7. 42,6% S-(-)-7.-5. 76,1%
8.	—	—	R-(+)-8. <0,5% S-(-)-8.-3. 3,9%	—	R-(+)-8.-5. 12,7% S-(-)-8. 3,1%
9.	R-(+)-9. 45,7% S-(-)-9.-1. 48,2%	R-(+)-9.-2. 2,6% S-(-)-9. 2,6%	R-(+)-9. 16,6% S-(-)-9.-3. 37,9%	—	R-(+)-9.-5. 4,4% S-(-)-9. <0,5%
10.	R-(+)-10.-1. 3,4% S-(-)-10. 12,8%	—	R-(+)-10.-3. 9,7% S-(-)-10. 17,8%	—	R-(+)-10.-5. 30,8% S-(-)-10. 32,2%

As it is anticipated, the chiral reagent 5 has proved to be a suitable reagent in all cases but the racemic compound 6. Previously the compound 5 has been successfully employed[10-13] for the enantiomeric separation of 7-10.

Although the primary aim of our investigation was to study the molecular chiral recognition in supercritical solvents, it was remarkable that the extent of chiral differentiation for the pairs of compounds 6.-1., 6.-3., 7.-5., 9.-1., 9.-3.,10.-1., 10.-3. and 10.-5. may render the enantiomeric separation possible even in preparative scale, particularly considering that the separation of enantiomeric mixtures can be carried out practically without loss. Thus it is possible that in resolutions done in supercritical solvents nearly the full scale

of resolution agents can be employed, or a resolution agent can be employed in a wider range than it was previously assumed.

1. 2.06 g of (0.010 mole) racemic 6 and 0.6 g (0.005 mole) of R-(+)-1, 2.0 g of Perfilt and 10 mL of methanol were mixed then evaporated. The residue was extracted with supercritical carbon dioxide. The temperature of the extract was set to 40°C and the quantity of carbon dioxide used for extraction was 150-200g, depending on the enantiomeric mixture. After the removal of the carbon dioxide, 0.8g S-(+)-6 was obtained, $[\alpha]_D$ =+21.0 (c=1, methanol). 20 mL of methylene chloride and 10 mL of 5N hydrochloric acid was added to the residue; the aqueous phase was further extracted with 2x20 mL of methylene chloride. The combined organic phases were evaporated to give 0.8g of R-(-)-6 $[\alpha]_D$ =-25.0 (c=1, methanol).

2. Carrying out the procedure analogously to the above described method with 1.68g (0.01 mole) of racemic 7 and 0.9g (0.005 mole) of S-(+)-5, 0.8g of 1R-(+)-7 $[\alpha]_D$ =+35.4 (c=1, chloroform) was obtained from the extract, whereas 0.6g of 1S-(-)-7,$[\alpha]_D$ =-63.4 was obtained.

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