Tetrahedron Vol. 41, No. 14, pp. 2841 to 2845, 1985
Printed in Great Britain

0040–4020/85 $3.00 + .00

DIASTEREOISOMERIC INTERACTIONS AND SELECTIVE REACTIONS IN SOLUTIONS OF ENANTIOMERS

E. Fogassy, F. Faigl and M. Ács*
Department of Organic Chemical Technology, Technical University Budapest, XI. Müegyetem rkp. 3/5, H-1521, Hungary

(*Received in UK* 31 *May* 1984)

Abstract As a consequence of homo- and heterochiral interactions in solutions of enantiomer mixtures selective reactions and separations can be achieved. Possibilities of selective separations and their characteristic properties were studied. On the basis of the common features of the investigated procedures selective separations can be planned.

In the field of practical stereochemistry, application of instrumental analysis (IR, NMR spectroscopy, differential scanning calorimetry, etc.)[1] produce more and more results concerning the existence, formation and behaviour and selective reactions of associates formed from enantiomers.[2] The binary phase diagrams prove that in solid phase formation of "molecule compounds" [$(DL)_n$ or D_n and L_n] occur, as a result of second order bond forming tendency of optical isomers with their mirror image isomers (heterochiral) or with themselves (homochiral interactions).[3] In order to get either one of the crystalline forms (or the other one), formation of an associate that consists of only "L" or of "D" isomers (conglomerates) or of the 1 : 1 mixtures (racemate) is necessary (at least in the "last" moment before precipitation), i.e. optical isomers may react in a selective way with each other.

In case of enantiomers of true racemates, in solution of mixtures in ratio different from 1 : 1, associates containing either the enantiomer in excess or both isomers in a 1 : 1 ratio may be produced at the same time.

Among the published papers, there are only a few in which the mentioned anomalies can only be explained by assuming di- or polymer associates, formed as a result of homo- and heterochiral interactions.

In these reactions under the same conditions (1) different stereostructures can be generated from the racemate than from the optically active isomers,[4] (2) rate constants for racemate or for optical isomers are different.[5]

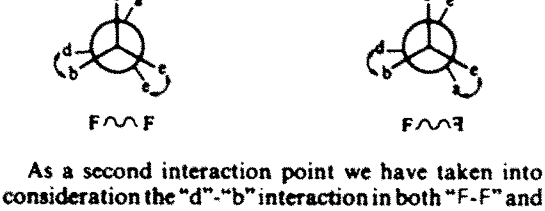
Associates formed in solution have a rather short lifetime, therefore they can be detected only with difficulty and they are supposed to be in equilibrium with each other. Their concentration may depend on the properties of the compound, on the concentration of the dissolved materials, and on analytical characteristics of the environment. Their properties differ from each other and from the dissolved molecules of the given compound.

Differences between dimer associates arising from a chiral compound generate from the differences in the secondary bonds. In a dimer there should be an interaction in which at least at three points (or one surface) attractive forces or non-hindered packing facilities are present.[6]

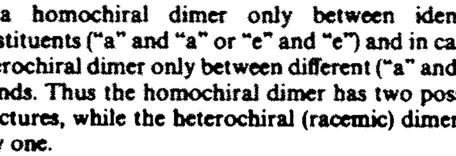
"Molecule formation" produced as a result of homo- and heterochiral interactions, are diastereoisomers of each other (Eq. 1) therefore they are different and can be separated. In the case of a chiral compound having only one asymmetric centre, the structure of associates is determined by the substituents attached to the chiral centre.

$$\text{enantiomers}\left\{\begin{array}{l} \text{F} + \text{F} \rightleftharpoons \text{FF} \\ \text{ꟻ} + \text{ꟻ} \rightleftharpoons \text{ꟻꟻ} \end{array}\right. \left.\begin{array}{l} \\ \\ \text{F} + \text{ꟻ} \rightleftharpoons \text{Fꟻ} \end{array}\right\} \text{diastereoisomers} \quad (1)^{\dagger}$$

Combining the isomers "F" and "ꟻ" of a compound with one chiral centre [carbon atom (C_{abde})] formation of the following associates or their rotamers can be expected, supposing the strongest interaction occurs between the ligands "b" and "d"



or for clarity with a Newman-like projection:



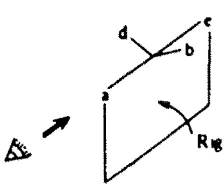
As a second interaction point we have taken into consideration the "d"-"b" interaction in both "F-F" and "F-ꟻ" combinations, thus the third attachment occurs in a homochiral dimer only between identical substituents ("a" and "a" or "c" and "c") and in case of heterochiral dimer only between different ("a" and "c") ligands. Thus the homochiral dimer has two possible structures, while the heterochiral (racemic) dimer has only one.

When the chiral centre is a part of a ring or a ring system, the structure of a dimer depends on the presence

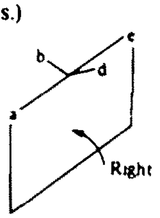
---

[†] Symbols "F" and "ꟻ" represent enantiomer relationship, "FF", "F ꟻ" and "ꟻ ꟻ" dimer associates.

or on the lack of the attachment of diastereotop surfaces (left side or right side, for clarity) of enantiomers. (We defined the sides, as the figure shows.)



F



ꟻ

Thus, combining the homo- and heterochiral isomers, nine types of dimer associates can be formed (F_rF_r, F_rF_l, F_lF_l and so on). For illustration let us examine right–left side interactions, which have been established in "F-F" and "F-ꟻ" dimers. In such a "molecule complex" the relative situation of the ligands "b" (consequently the ligands "d", too) are different. For clarity uniting the two ring planes, we have got a hypothetical one. Related to this hypothetical plane, ligands "b" (or "d"-s) are in "*cis*" position, in the dimer "F_r-F_l", and they have "*trans*" positions in the "F_r-$ꟻ_l$" dimer, and so on.

F_rF_l $F_rꟻ_l$

Right–left interactions.

If the compound has more than one chiral centre (axis, plane or helicity) the structure of associates depends mainly on the centre which connects with the most suitable substituents for resulting the strongest interactions. The interaction of molecules may be so strong that a dimer associate can be dissolved with half an equivalent of achiral reagent. For example in case of chrysanthemic acid (or permethrinic acid, **10**) a very strong secondary interaction occurs presumably between the vinyl group and the 3-membered ring, so the water insoluble free acid can be dissolved with half an equivalent amount of sodium hydroxide, in water. Resolution procedures for these compounds are very sensitive to the pH-shift. As a function of pH, using the same resolving agent either one or the other isomer forms the less soluble diastereoisomeric salt.[9]

Associates consisting of homo- and heterochiral isomers react with achiral reagents at different rates and their distribution between two phases differ, too. Consequently associates arising from an enantiomer mixture having a different ratio than 1 : 1 allow the selective separation of the enantiomer in excess from the racemate, even without application of another chiral agent. For illustration let us show schematically the equilibrium model of the selective separation (precipitation). During the course of the procedure a solution of the achiral salt of an enantiomer mixture is reacted with less than equivalent achiral reagent having the same chemical constitution as the optically active compound (Fig. 1). For explanation of the successfully accomplished selective precipitations we assumed the formation of diastereoisomeric associates, though their actual concentration can be very small. The separation is more effective, when the heterochiral interaction is stronger, than that of the homochiral, and the solubilities of enantiomers are greater than that of the racemate (or vice versa). In such a case the precipitation contains a nearly pure racemic mixture (or enantiomer). The extent of the separation ($S_e = k \times t$, where k is the chemical yield, t is the optical purity) depends on the initial optical purity (t_o), the solubilities of the enantiomers (K_{se}), and the solubility of the racemic form (K_{sr}).

In the case of selective separations accomplished with achiral auxiliary reagents, S_e depends on the pH and on the dissociation constant of the enantiomers (K_b), too.

The most widely applied method of enantiomer purification is based upon fractional crystallization

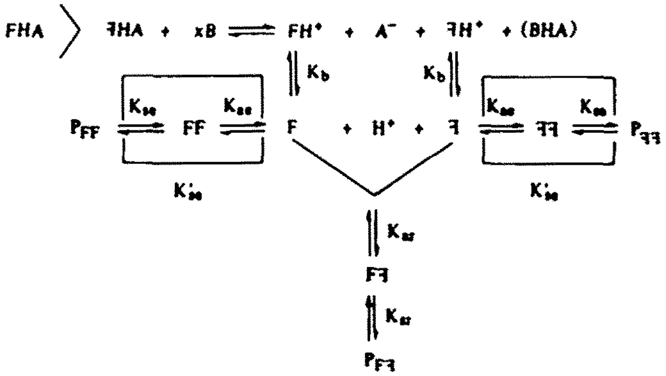
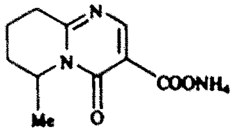
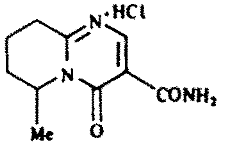
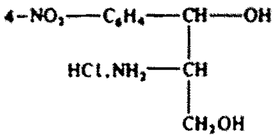
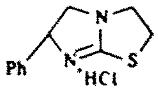
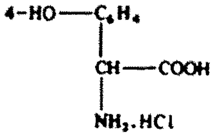
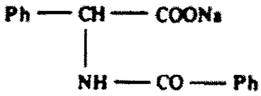
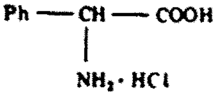
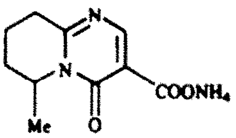
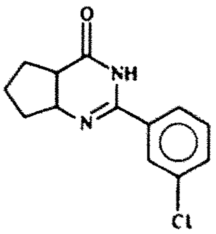
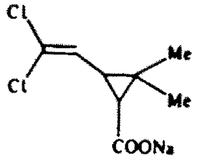


Fig. 1. Equilibrium model of selective precipitation. Meaning of symbols: FHA, ꟻHA, enantiomer salts; B, achiral base; F, ꟻ, enantiomers; FF, ꟻꟻ, Fꟻ, dimer associate; K_a, associate constants of e: enantiomers, r: racemate; K_s, solubility of e: enantiomers and r: racemate; P_r, amount of the precipitated base; K_b, dissociation constant of enantiomers.

$$K_{ar} = \frac{[Fꟻ]}{[F][ꟻ]}; \quad K_{ae} = \frac{[FF]}{[F][F]} = \frac{[ꟻꟻ]}{[ꟻ][ꟻ]}; \quad K_b = \frac{[F][H^+]}{[FH^+]} = \frac{[ꟻ][H^+]}{[ꟻH^+]}$$

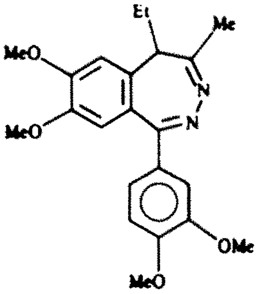
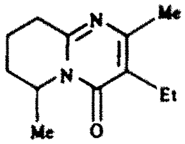
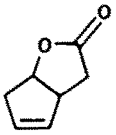
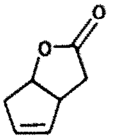
$$K_{sr} = [Fꟻ]_{saturated}; \; K'_{se} = [F]_{sat} = [ꟻ]_{sat}.$$

Table 1. Models, methods, solvents, auxiliary reagents and results of the investigated selective separations

No.	Model	Method	Solvent	Aux. reag.	t	k	S_e	Ref.
1		C	H_2O	HCl	0.76^f	0.866	0.658	8
2		C	H_2O	NH_4OH	0.65^f	0.84	0.546	9
3	 $4\text{-}NO_2{-}C_6H_4{-}CH(OH){-}CH(NH_2\cdot HCl){-}CH_2OH$	A	H_2O		0.95^f	0.95	0.900	8
4		C	H_2O	NaOH	0.988^f	0.70	0.700	10
5	 $4\text{-}HO{-}C_6H_4{-}CH(NH_2\cdot HCl){-}COOH$	C	H_2O	NaOH	0.91^f	0.73	0.667	9
6	 $Ph{-}CH(NH{-}CO{-}Ph){-}COONa$	C	H_2O	HCl	0.812^f	0.862	0.700	9
7	 $Ph{-}CH(NH_2\cdot HCl){-}COOH$	C	H_2O	NaOH	0.800^f	0.997	0.798	9
8		D	H_2O and $CHCl_3$	HCl	0.800^e	0.800	0.640	8
9		A	EtOH	–	0.600^f	1.20	0.720	9
10		C	H_2O	HCl	0.340^e	1.00	0.340	9

(continued)

Table 1. (*contd.*)

No.	Model	Method	Solvent	Aux. reag.	t	k	S_e	Ref.
11		A	EtOAc		0.956^r	0.254	0.245	9
12		B	—		0.780^e	0.934	0.729	9
13		B		—	0.800^e	0.481	0.385	7
14		E	EtOH	NaOH	0.656^r	0.998	0.656	11

Meaning of symbols: S_e extent of separation $= k \times t$ where k, chemical yield of the form having undergone phase transition, in per cent of the given form's amount in the initial sample and t, optical purity, when the enantiomer in excess undergoes phase transition. 1-o.p. in case of the racemic form changes the phase superscripts: r, racemic; e, enantiomeric form changes the phase.

(method A),[3] which can be made selective with the aid of solubility diagrams.

The diastereoisomer associates can be separated in the same selective way, if a considerable melting point difference exists between the racemate and the enantiomers (crystallization from melt, binary phase diagrams are requested; method B).[7] The selectivity of acid–base reactions carried out using a non-equivalent amount of achiral agent and accompanied by a phase alteration can be very great (selective precipitation, method C),[10] and selective liberation combined with extraction (method D).[8] If the ratio of reaction rate constants for diastereoisomers differs from the 1 : 1, then chemical reactions can be accomplished in a selective way (method E).[9]

In order to find the common features necessary for generalization and for the planning of selective separations, 14 different cases have been investigated (Table 1). As we have stated before, the efficiency of separation depends on the initial optical purity (t_o). The schematized dependence of the optical purity (t) on t_o for the fractions obtained from the two distinct phases (precipitation and mother liquor) can be seen in Fig. 2.

The separation is the most efficient at an initial optical purity of 50%, therefore the obtained results are the most reliable in this range, so for the calculation of S_e we have taken the efficiency of the separation that was started from $t_o = 50\%$ (Table 1).

At a composition of 50% the equilibrium occurring in

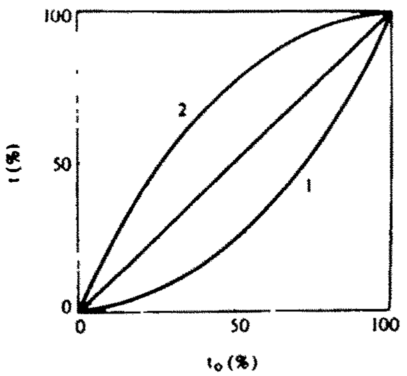
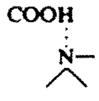
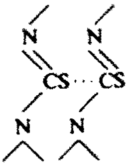


Fig. 2. The optical purity (t) of the fractions (precipitation, line 1, mother liquor, line 2) obtained by selective precipitation as a function of initial optical purity (t_o) (schematized case).

Table 2. Efficiency of selective separations

Model	1	2	3	4	5	6	7
$1+\log S_e$	0.8182	0.7372	0.9542	0.8451	0.8241	0.8451	0.9020
$\lvert\Delta\Sigma\sigma^*\rvert$	0.4866	0.3600	1.0906	0.6208	0.7870	0.8089	1.070
"a"-"e" interaction			$PhNO_2 \cdots HO$		$COOH \cdots HO$	$(PhCO \cdots Ph)_2$	$NH_3^+ \cdots {}^-OOC$

$1+\log S_e$, $\Delta\Sigma\sigma^*$ and the interacting groups "a"-"e" in the racemic dimer. For models see Table 1.

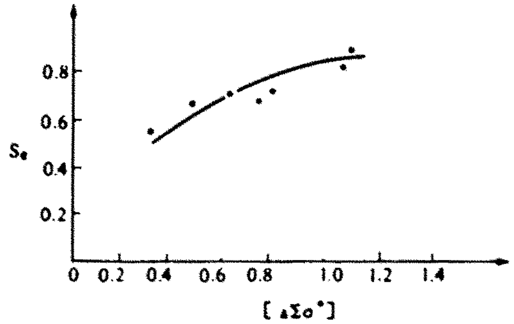


Fig. 3. Efficiency of the selective separation as a function of $\lvert\Delta\Sigma\sigma^*\rvert$. The equation of the regression line is Eq. 5.

$$1+\log S_e = a\Delta\Sigma\sigma^* + b \qquad (5)$$

where for selective precipitation: $a = 0.225$, $b = 0.679$, standard deviation $= 0.068$, $r = 0.914$, number of data $= 7$.

the solution can be shifted to the right-hand side of Eq. 2 by removing one of the fractions.

3F + ꟻ ⇌ Fꟻ + FF (2)†

The basis of separation is the difference in physical and chemical properties of diastereoisomers, which is generated from the relative positions of the substituents attached to the chiral centre. The position of substituents are influenced by steric and electronic parameters. In our mathematical statistical model of resolution procedure via diastereoisomeric salt formation,[12] the efficiency of resolution is mainly determined by the electronic parameters, which we have characterized by the Taft σ^* constant (Eq. 3).[14]

$$S = f(\Delta\Sigma\sigma^*) \qquad (3)$$

As in the case the relation of associates is also diastereoisomeric we have tried to arrange our data by using the Taft σ^* values. The postulated relative position of the enantiomers have been studied during separation procedures carried out principally in the same way as seen in Table 2. The σ^* values of the groups suitable for interactions and attached to the chiral centre have been summed and the difference of these sums was formed (Eq. 4),

$$\lvert\Sigma(\sigma^*_j + \sigma^*_{j'}) - \Sigma(\sigma^*_{j'} + \sigma^*_{j+1})\rvert > 0 \qquad (4)$$

where "j" is a variant depending on the number of interacting groups, although in fact the difference is derived from the $\Delta\Sigma\sigma^*$ of the "third" "a"-"e" or "a"-"a" interaction.

During the selective precipitation in the crystalline phase always the fraction having the associate of higher value was in excess (Table 2). It can be concluded drawing the efficiency as a function of $\Delta\Sigma\sigma^*$ (Fig. 3) that separation is the more selective the higher the difference is. On the basis of the above discussion it can be concluded that selective separation of partially resolved enantiomer mixtures can be planned with the aid of analogous principles to those of the resolution procedures.[13]

REFERENCES

[1] *Stereochemistry: Fundamentals and Methods* (Edited by H. B. Kagan), Vols 1–2. G. Thieme, Stuttgart (1977).

[2][a] M. I. Kabacsnyik, T. A. Masztrjukova, E. I. Fegyin, M. Sz. Vajszberg, L. L. Morozov, P. V. Petrovszkij and A. E. Sipov, *Tetrahedron* **32**, 1719 (1976); [b] T. Williams, G. Pitcher, P. Bommer, J. Gutzwiller and M. Uskokovic, *J. Am. Chem. Soc.* **91**, 1871 (1969); [c] A. Horeau and J. P. Guetté, *Tetrahedron* **31**, 1923 (1974); [d] D. P. Craig and D. P. Mellor, *Topics in Current Chemistry*, Vol. 63, pp. 1–48 (1976); [e] E. Fogassy, F. Faigl and M. Ács, *Tetrahedron Lett.* **22**, 3093 (1981).

[3] J. Jacques, A. Collet and S. H. Wilen, *Enantiomers, Racemates and Resolutions*. Wiley, New York (1981).

[4] H. Wynberg and B. Feringa, *Tetrahedron* **32**, 2831 (1976).

[5] R. Chang and S. I. Weissman, *J. Am. Chem. Soc.* **89**, 5968 (1967).

[6] A. Ogston, *Nature* **162**, 963 (1948).

[7] Hung. Patent 181 416 (L. Töke, E. Fogassy, M. Ács and P. Bencsik, 1979, CHINOIN Pharmaceutical and Chemical Works Ltd.).

[8] E. Fogassy, M. Ács and I. Hermecz, *Per. Pol.* **20**, 263 (1976).

[9] Unpublished results.

[10] E. Fogassy, M. Ács, J. Felméri and Zs. Aracs, *Per. Pol.* **20**, 247 (1976).

[11] Hung. Patent 177 583 (L. Töke, E. Fogassy, G. Szabó, M. Ács, L. Nagy and L. Árvai, 1978, CHINOIN Pharmaceutical and Chemical Works Ltd.) *Chem. Abstr.* **96**, 6268u.

[12] E. Fogassy, A. Lopata, F. Faigl, F. Darvas, M. Ács and L. Töke, *Tetrahedron Lett.* **21**, 647 (1980).

[13] E. Fogassy, F. Faigl and M. Ács, *Tetrahedron* **41**, 2837 (1985).

[14] C. Hansch, A. Leo, S. H. Unger, K. H. Kim, D. Nikitani and E. J. Lien, *J. Med. Chem.* **16**, 1207 (1973).

---

† Recall that this situation is an analogous one to an optical resolution procedure using a non-equivalent resolving agent.