Pergamon

Tetrahedron: *Asymmetry* 12 (2001) 2927–2930

TETRAHEDRON:
ASYMMETRY

Probability of spontaneously resolvable conglomerates for racemic acid/racemic amine salts predicted on the basis of the results of diastereomeric resolutions

Kazushi Kinbara, Yoshiyuki Tagawa and Kazuhiko Saigo*

Department of Integrated Biosciences, Graduate School of Frontier Sciences, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-8656, Japan

Received 1 September 2001; accepted 9 November 2001

Abstract—The salts of racemic acids with racemic amines, of which the enantiopure component is a good resolving agent for the corresponding counterpart in diastereomeric resolution, have an extremely high tendency to be conglomerates: the results of diastereomeric resolutions are highly informative for the prediction of conglomerates, which can be enantioseparated by preferential crystallization developed independently from diastereomeric resolution over one and a half centuries. © 2002 Elsevier Science Ltd. All rights reserved.

The discrimination of chirality of a racemate was first demonstrated by Pasteur, who found that crystals of racemic ammonium sodium tartrate tetrahydrate could be manually separated into both enantiomers.[1] This phenomenon, known as spontaneous resolution, is of great interest in relation to many topics, for example the origin of the homochirality of terrestrial life,[2,3] non-linear optics,[4] absolute asymmetric synthesis,[5] etc. Spontaneous resolution is also quite fascinating in that no internal or external chiral auxiliary is required for the resolution of a racemate. Due to this advantage, this phenomenon has been successfully applied to the resolution of natural and non-natural chiral compounds by seeding (preferential crystallization).[6]

However, there is a serious limitation to the application of preferential crystallization, since it is believed that only 5–10% of crystalline racemates are conglomerates, which can be resolved into their pairs of enantiomers in this way; moreover the actual proportion of conglomerates is much less than this as it has been overestimated due to a bias.[7,8] Furthermore, all of the known conglomerates appear to have been discovered completely by accident.

Is there then any way to improve this situation and to find conglomerates with a high probability? We report herein that the salts of racemic acids with racemic amines show an extremely high tendency to be conglomerates when the corresponding enantiopure form of the acid and/or amine is an efficient resolving agent for its counterpart in diastereomeric resolution.[7,9]

In our studies concerning enantioseparation by preferential crystallization,[10,11] we found that the salts of racemates and achiral derivatizing agents are conglomerates with a higher probability than are ordinary racemates when the derivatizing agent has a similar molecular length and/or shape to the racemate (for example, when the racemate is an amine, the agent should be an acid, and vice versa) and that the resultant conglomerate crystals have in common a helical hydrogen-bond network (2_1 column) consisting of units of two acid molecules and two amine molecules, rather than a centrosymmetric hydrogen-bond network. On the other hand, our continuing studies on diastereomeric resolution (the resolution of a racemate with an enantiopure derivatizing agent) showed that high resolution efficiencies[12] are achieved when the resolving agent has a similar molecular length to the racemate, and that the less-soluble (deposited) salt crystals have a 2_1 column, also consisting of two pairs of the acid and amine molecules.[13] These studies led us to recognize that the molecular-structural requirements for achieving successful resolution with respect to both derivatizing agents in preferential crystallization and resolving agents in diastereomeric resolution are very similar to each other. Taking into account this similar-

---

* Corresponding author. E-mail: saigo@chiral.t.u-tokyo.ac.jp

PII: S0957-4166(01)00527-4

ity, we were interested in what happens when a *racemic* acid (RA) is allowed to form a crystalline salt with a *racemic* amine (RB).

The possible crystal structures for a salt in a diastereomeric resolution are illustrated in Fig. 1b. It is possible to form either a pair of a less-soluble salt (L_a) and a more-soluble salt (M_a), or a double salt (D_a). The achievement of high efficiency in the diastereomeric resolution means that L_a must be much more stable than M_a, and still less that D_a is not formed. Although a *pseudo*-centrosymmetric hydrogen-bond network is frequently found in diastereomeric double salts,[14] that no D_a is formed in this case indicates that D_a having a *pseudo*-centrosymmetric hydrogen-bond network is much less stable than L_a and M_a having 2_1-symmetric hydrogen-bond networks (see Fig. 1). The plausible crystal structures for the salt of a racemic acid and a racemic amine (RA–RB salt) are shown in Fig. 1b. Of these crystal structures, i.e. conglomerates (C_b), double salt (D_b), racemic compounds (R_b), and solid solution (S_b), the possibility of S_b would be likely to be so low as to be negligible, as was recognized for ordinary racemates. It is noteworthy that C_{bL}, C_{bM}, and D_b in Fig. 1b coincide completely with L_a, M_a, and D_a in Fig. 1a, respectively, and that for R_b there are two possible crystal structures; R_{bA} consists of a 2_1-symmetric hydrogen-bond network and R_{bB} composes a centrosymmetric hydrogen-bond network. Here, if the corresponding enantiopure form of a component of a RA–RB salt is a good resolving agent for its counterpart in a diastereomeric resolution, C_{bL} should be more stable than C_{bM} and D_b as L_a is more stable than M_a and D_a. In addition, 2_1-symmetric C_{bL} would be expected to be more stable than centrosymmetric R_{bA} as well, as 2_1-symmetric L_a is more stable than *pseudo*-centrosymmetric D_a. Under such conditions (C_{bL} is more stable than C_{bM}, D_b, and R_{bA}), in order for a conglomerate to be formed, it is simply necessary that C_{bL} is more stable than R_{bB}. This analysis strongly suggests that the probability of being C_{bL} increases for the crystal deposited from a supersaturated RA–RB salt solution, namely the crystal has a high tendency to be a conglomerate, when the corresponding enantiopure acid and/or amine component of the RA–RB salt can be successfully applied to the diastereomeric resolution of its counterpart.

On the basis of these considerations, we checked whether RA–RB salts are conglomerates or not. Arylglycolic acid/1-arylethylamine salts were selected as the subject RA–RB salts in the present study, since the

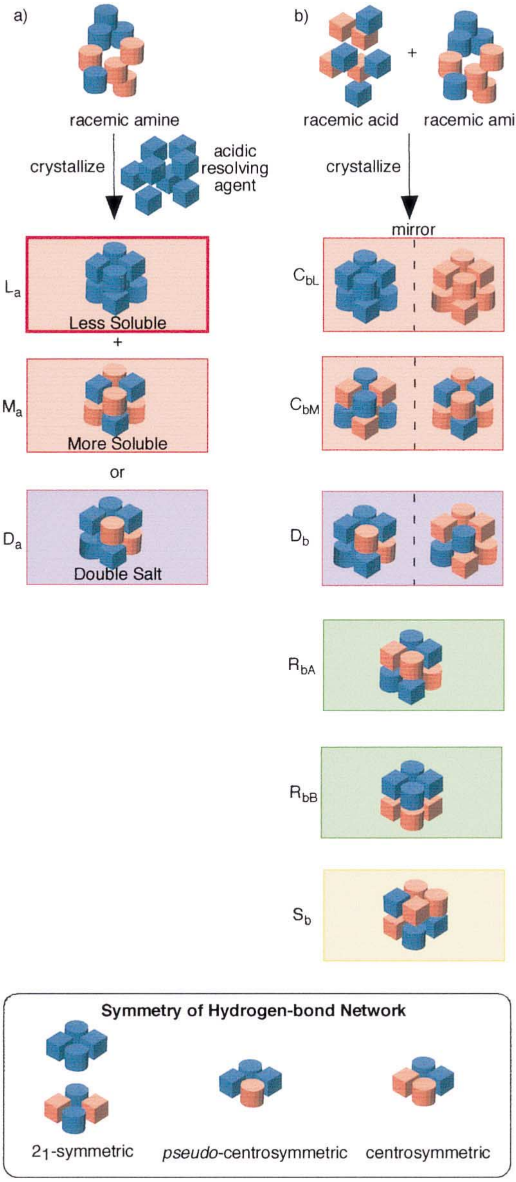
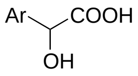


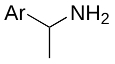
Fig. 1.

Figure 1. (a) Possible types of crystal structure of a salt formed during the diastereomeric resolution of a racemic amine with an enantiopure acidic resolving agent. The blue and red cylinders represent the racemic amine molecules, and blue cubes represent the acid molecules. The figures at the bottom are cartoons for hydrogen-bond networks, and do not reflect the precise symmetry elements. L_a: the less-soluble diastereomeric salt. M_a: the more-soluble diastereomeric salt. D_a: a double salt, which contains the acidic-resolving agent and both enantiomers of the racemic amine in a unit cell. (b) Plausible types of crystal structure of a salt consisting of a racemic acid and a racemic amine (RA–RB salt). The cubes and cylinders represent the acid and amine molecules, respectively. C: a conglomerate in which one of the enantiomers of the acid and of the amine are included in a unit cell. In this case two diastereomeric conglomerates (C_{bL} and C_{bM}) are possible. D_b: a diastereomeric double salt, in which the acid or amine is racemic while the other component (the amine or acid) is spontaneously resolved. The figure shows one of the possible packing modes for diastereomeric double salts. R_{bA}: a racemic compound containing the centrosymmetric hydrogen-bond network. The figure shows one possible packing mode. R_{bB}: a racemic compound containing the 2_1-symmetric hydrogen-bond network. The figure shows one possible packing mode. S_b: a solid solution of the racemic acid and amine, occupying irregular positions.

diastereomeric resolution of this combination has been investigated systematically in our laboratory.[13,15] In the case of the RA–RB salts of arylglycolic acids **1**–**5**/1-phenylethylamine **6**, both the enantiopure acid and amine are good resolving agents for their counterparts, while in the case of the RA–RB salts of 2-naphthylglycolic acid **5**/1-arylethylamines **7**–**14**, 2-naphthylglycolic acid is at least an excellent resolving agent for the amines. The crystal modes of these RA–RB salts are listed in Table 1 along with the efficiencies of the diastereomeric resolutions. As is shown here, very surprisingly the proportion of the crystal structures of the RA–RB salts that are conglomerates is over 50%; this value is much higher than that normally estimated for independent racemates (5–10%).[7,8] From these results and the theoretical considerations outlined above, it is strongly suggested that the salt of a racemic acid and a racemic amine has a high probability of being a conglomerate when the corresponding enantiopure acid and/or amine component is a good resolving agent for its counterpart.

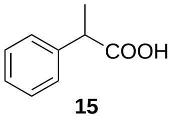


1: Ar = C_6H_5
2: Ar = p-MeC_6H_4
3: Ar = p-ClC_6H_4
4: Ar = p-$MeOC_6H_4$
5: Ar = 2-$C_{10}H_7$
(2-Naphthyl)

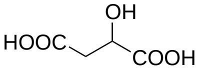


6: Ar = C_6H_5
7: Ar = p-MeC_6H_4
8: Ar = p-EtC_6H_4
9: Ar = p-PrC_6H_4
10: Ar = p-cyclohexyl-C_6H_4
11: Ar = p-ClC_6H_4
12: Ar = p-BrC_6H_4
13: Ar = p-$MeOC_6H_4$
14: Ar = 1-$C_{10}H_7$
(1-Naphthyl)

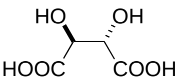
This high tendency of being a conglomerate was also realized upon re-investigating an early study on RA–RB salts carried out by Jacques et al.;[18] they examined the crystal modes of RA–RB salts for all combinations of 16 kinds of acids and nine kinds of amines. Since Jacques et al. have not made no mention of their diastereomeric resolutions, we re-investigated the correlation between the results of the diastereomeric resolutions and the crystal modes of these RA–RB salts. As a result, it was found that for 24 RA–RB salts among the combinations successful diastereomeric resolutions are reported so far by using the corresponding enantiopure acid and/or amine component as a resolving agent for its counterpart, and that 11 of them (**1·22**, **1·23**, **15·6**, **15·22**, **16·6**, **17·23**, **17·24**, **18·25**, **19·6**, **20·6**, **21·6**) are conglomerates. This means that the proportion that are conglomerates is 46% for those RA–RB salts satisfying the criterion that the corresponding enantiopure acid and/or amine is a good resolving agent for its counterpart in a diastereomeric resolution.



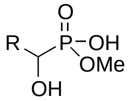
15



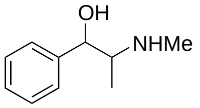
16



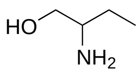
17



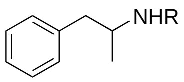
18: R = C_6H_5
19: R = 2,4-$Cl_2C_6H_3$
20: R = p-$NO_2C_6H_4$
21: R = Cl_3C



22



23



24: R =Me
25: R = H

Table 1. Crystal modes of RA–RB salts of 1-arylglycolic acid/1-arylethylamine

Acid	Base	Type of racemate	Determination method[a]	Efficiency of diastereomeric resolution[b] by enantiopure component	
				Acid	Base
1	**6**	R_{bB}[16]	XRC	0.66	0.36
2	**6**	C_{bL}	XRC	0.50	0.41
3	**6**	C_{bL}	XRC	0.59	0.64
4	**6**	R_{bB}	XRC	0.62	0.76
5	**6**	R_{bA}	XRC	0.70	0.54
5	**7**	C_{bL}	XRC	0.77	0.50
5	**8**	R_b or D_b	XRPD	0.61	–
5	**9**	C_{bL}	XRPD	0.79	–
5	**10**	R_{bB}	XRC	0.46	–
5	**11**	C_{bL}	XRC	0.50	0.59
5	**12**	C_{bL}	XRC	0.75	–
5	**13**	R_{bA}	XRC	0.75	–
5	**14**	C_{bL}	XRPD	0.56	0.46

[a] XRC: X-ray crystallographic analysis;[17] XRPD: X-ray powder diffraction.

[b] Solvent: aqueous alcohol.

The study presented shows that the combination of a racemic acid and a racemic amine, where the corresponding enantiopure compound is a good resolving agent for its racemic counterpart in a diastereomeric resolution, has a very high probability of being a conglomerate. This implies that preferential crystallization and diastereomeric resolution are fundamentally linked to each other. Moreover, it also shows that on the basis of the result of a diastereomeric resolution, the concurrent separation of a racemic acid and a racemic amine into the two pairs of enantiomers can be achieved by preferential crystallization. The present result represents not only a potential method for the discovery of conglomerates, but also a bridge between preferential crystallization and diastereomeric resolution, which have undergone independent development for over one and a half centuries.

Acknowledgements

This work was supported by Grants-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture of Japan.

References

1. Pasteur, L. C. R. *Acad. Sci.* **1848**, *26*, 535–538.
2. Bonner, W. *Origins Life Evol. Biosphere* **1994**, *24*, 63–78.
3. Kondepudi, D. K.; Laudadio, J.; Asakura, K. *J. Am. Chem. Soc.* **1999**, *121*, 1448–1451.
4. *Non-linear Optical Properties of Organic Molecules and Crystals*, Zyss, J.; Chemla, D. S., Eds.; Academic: Orlando, 1987; Vols. 1 and 2.
5. Penzien, K.; Schmidt, G. M. J. *Angew. Chem.* **1969**, *81*, 628.
6. Jungfleisch, M. E. *J. Pharm. Chim.*, 5 ème Série, **1882**, *5*, 346–357.
7. Jacques, J.; Collet, A.; Wilen, S. H. *Enantiomers, Racemates, and Resolutions*; Krieger Publishing Company: Malabar, Florida, 1994.
8. Brock, C. P.; Dunitz, J. D. *Chem. Mater.* **1994**, *6*, 1118–1127.
9. Pasteur, L. C. R. *Acad. Sci.* **1853**, *37*, 162–166.
10. Saigo, K.; Ogawa, S.; Kikuchi, S.; Kasahara, A.; Nohira, H. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 1568–1573.
11. Kinbara, K.; Hashimoto, Y.; Sukegawa, M.; Nohira, H.; Saigo, K. *J. Am. Chem. Soc.* **1996**, *118*, 3441–3449.
12. Defined as the product of the yield of the diastereomeric salt (based on a half amount of the racemate) and the e.e. of the resolved racemate.
13. Kinbara, K.; Sakai, K.; Hashimoto, Y.; Nohira, H.; Saigo, K. *J. Chem. Soc., Perkin Trans. 2* **1996**, 2615–2622.
14. Kinbara, K.; Saigo, K.; unpublished data.
15. Kinbara, K.; Harada, Y.; Saigo, K. *J. Chem. Soc., Perkin Trans. 2* **2000**, 1339–1347.
16. Diego, H. L. *Acta Crystallogr., Sect. C* **1995**, *51*, 935–937.
17. Since single crystals of the RA–RB salts were of low quality, a sufficient number of reflections could not be measured for the complete full refinement. For, **2·6**, **3·6**, **5·6**, **5·7**, and **5·11**, the unit cell parameters as well as the space group coincide with the corresponding less-soluble salts in our previous studies.[13,15] The temporary data for these analyses are as follows: **2·6**, $C_{17}H_{21}NO_3$, $M=287.36$, orthorhombic, $a=8.417(4)$, $b=27.290(10)$, $c=6.850(4)$ Å, $V=1573.4(11)$, Space group $P2_12_12_1$, $Z=4$, $\mu(\text{Cu K}\alpha)=0.669\ \text{cm}^{-1}$, $R=0.085$ for 1412 unique reflections (1514 measured reflections); **3·6**, $C_{16}H_{18}ClNO_3$, $M=307.78$, orthorhombic, $a=6.869(1)$, $b=8.428(1)$, $c=27.030(1)$ Å, $V=1564.8(11)$, space group $P2_12_12_1$, $Z=4$, $\mu(\text{Mo K}\alpha)=0.253\ \text{cm}^{-1}$, $R=0.054$ for 4503 unique reflections (5361 measured reflections); **4·6**, $C_{17}H_{21}NO_4$, $M=303.36$, monoclinic, $a=8.346(4)$, $b=6.883(2)$, $c=28.031(13)$ Å, $\beta=94.94(2)°$, $V=1604.3(9)$, space group $P2_1/n$, $Z=4$, $\mu(\text{Mo K}\alpha)=0.089\ \text{cm}^{-1}$, $R=0.068$ for 1504 unique reflections (3642 measured reflections); **5·6**, $C_{20}H_{21}NO_3$, $M=323.39$, triclinic, $a=5.311(4)$, $b=9.080(12)$, $c=18.03(3)$ Å, $\alpha=81.622(8)°$, $\beta=87.732(8)°$, $\gamma=83.758(8)°$, $V=854.7(19)$, space group $P\bar{1}$, $Z=2$, $\mu(\text{Mo K}\alpha)=0.084\ \text{cm}^{-1}$, $R=0.063$ for 2040 unique reflections (3182 measured reflections); **5·7**, $C_{21}H_{23}NO_3$, $M=337.42$, orthorhombic, $a=6.8610(5)$, $b=8.4460(9)$, $c=31.567(3)$ Å, $V=1829.2(3)$, space group $P2_12_12_1$, $Z=4$, $\mu(\text{Mo K}\alpha)=0.081\ \text{cm}^{-1}$, $R=0.080$ for 1585 unique reflections (6331 measured reflections); **5·10**, $C_{26}H_{31}NO_3$, $M=405.54$, monoclinic, $a=8.762(1)$, $b=6.7711(8)$, $c=37.063(4)$ Å, $\beta=90.354(9)°$, $V=2198.8$ (4), space group $P2_1/c$, $Z=4$, $\mu(\text{Cu K}\alpha)=0.627\ \text{cm}^{-1}$, $R=0.113$ for 2621 unique reflections (3899 measured reflections); **5·11**, $C_{20}H_{20}ClNO_3$, $M=357.84$, orthorhombic, $a=8.448(1)$, $b=31.182(6)$, $c=6.855(2)$ Å, $V=1805.8$ (5), space group $P2_12_12_1$, $Z=4$, $\mu(\text{Cu K}\alpha)=2.025\ \text{cm}^{-1}$, $R=0.093$ for 1567 unique reflections (1762 measured reflections); **5·12**, $C_{20}H_{20}BrNO_3$, $M=402.29$, orthorhombic, $a=6.916(2)$, $b=8.417(1)$, $c=31.371(6)$ Å, $V=1826.2(6)$, space group $P2_12_12_1$, $Z=4$, $\mu(\text{Mo K}\alpha)=2.276\ \text{cm}^{-1}$, $R=0.073$ for 1513 unique reflections (5040 measured reflections); **5·13**, $C_{21}H_{23}NO_4$, $M=353.42$, triclinic, $a=5.338(1)$, $b=9.015(2)$, $c=19.341(3)$ Å, $\alpha=91.62(2)$, $\beta=93.25(2)$, $\gamma=95.70(2)°$, $V=924.1(3)$, space group $P\bar{1}$, $Z=2$, $\mu(\text{Cu K}\alpha)=0.714\ \text{cm}^{-1}$, $R=0.067$ for 2293 unique reflections (3357 measured reflections).
18. Jacques, J.; Leclercq, M.; Brienne, M.-J. *Tetrahedron* **1981**, *37*, 1727–1733.