

Available online at www.sciencedirect.com



Tetrahedron: Asymmetry 15 (2004) 1073-1076

Tetrahedron: Asymmetry

Chiral discrimination controlled by the solvent dielectric constant

Kenichi Sakai,^{a,*} Rumiko Sakurai^a and Noriaki Hirayama^{b,*}

^aR & D Division, Yamakawa Chemical Industry Co., Ltd, Kitaibaraki 319-1541, Japan ^bBasic Medical Science and Molecular Medicine, Tokai University School of Medicine, Isehara 259-1193, Japan

Received 15 January 2004; accepted 4 February 2004

Abstract—Chiroselective molecular recognition accompanied by a change in configuration of a target substrate has been studied. (RS)- α -Amino- ε -caprolactam 1 was used as the target substrate to be resolved while *N*-tosyl-(*S*)-phenylalanine 2 was used as the chiral selector. The dielectric constant (ε) of the solvent was found to have a profound effect on the chiroselective molecular recognition. The specific chiral selector (*S*)-2 not only recognized both enantiomers (*R*)- and (*S*)-1 individually to be deposited as the less-soluble salt from the different solvent but also controlled the configuration and diastereomeric excess of the less-soluble diastereomeric salt by simple adjustment of the solvents dielectric constant. The chiroselective recognition mechanism was examined based on the crystal structures of the salts, (*S*)-1·(*S*)-2·H₂O and (*R*)-1·(*S*)-2, obtained from the resolution process. \bigcirc 2004 Elsevier Ltd. All rights reserved.

Diastereomeric salt formation using a resolving agent as a chiral selector, is one of the most useful methods for obtaining a target stereoisomer from its racemic mixture.¹ Since it is generally accepted that a specific chiral selector only acts on one of the stereoisomers and produces the less-soluble diastereomeric salt containing one stereoisomer, the opposite stereoisomer must therefore be recognized by the enantiomorph of the chiral selector. It seems that there is no way to change this one-toone situation from the viewpoint of general resolution chemistry. However, we found a quite unusual phenomenon, which meant that we should reconsider this common notion on chiral discrimination; the specific chiral selector not only recognized both enantiomers individually, to be deposited as the less-soluble salt from different solvents but also controlled their diastereomeric excess (% de) of the less-soluble diastereomeric salt by simply altering the dielectric constant (ε) of the solvent used.

During the development of a resolution process for (RS)- α -amino- ε -caprolactam 1² with *N*-tosyl-(S)-phenylalanine 2,³ we found that the configuration of the excess enantiomer in the less-soluble diastereomeric salt was variable dependent on the ε of the solvent used⁴ (Fig. 1). Based on this finding, we developed a practical



Figure 1.

^{*} Corresponding authors. Fax: +81-293-30-1181 (K.S.); e-mail addresses: sakai@yamakawa-chemical.co.jp; hirayamada@is.icc.u-tokai.ac.jp

Table 1. Resolution of (RS)-1 with (S)-2 in various solvents

Entry	Solvent	Dielectric	Solvent	Yield (%) ^b	Diastereomer	Absolute	Resolution
		constant (ɛ)	volume ^a [vs (RS)-1] (w/w)		excess (% de)	configuration	efficiency $(E)^{c}$
1	Chloroform	5	7	24	69	R	33
2	EDC	11	6	44	61	R	54
3	MIBK	13	45	63	41	R	52
4	2-PrOH	18	50	65	32	R	42
5	EtOH	24	32	70	7	R	10
6	89% 2-PrOH	25	11	60	29	R	35
7	85% 2-PrOH	27	10	55	22	R	24
8	90% EtOH	29	15	63	10	S	13
9	MeOH	33	10	32	93	S	60
10	81% EtOH	34	12	25	99	S	50
11	95% MeOH	35	16	16	92	S	29
12	DMF	37	27	28	90	S	50
13	74% EtOH	38	14	13	100	S	26
14	1,2-Ethandiol	39	43	38	99	S	75
15	DMSO	49	32	20	96	S	38
16	60% MeOH	51	11	10	95	S	19
17	55% MeOH	53	5	42	25	S	21
18	45% MeOH	58	8	49	3	S	3
19	30% EtOH	62	10	45	6	R	5
20	35% MeOH	63	6	16	13	R	4
21	10% MeOH	74	19	38	35	R	27
22	Water	78	18	31	28	R	17

^a Solvent volume is the minimum volume to obtain clear solution at 50 °C except for a case using 74% EtOH.

^b Yield is calculated based on a half amount of (RS)-1.

^cResolution efficiency (E, %) = yield (%) × diastereometric excess $(\% \text{ de}) \times 0.02$.

continuous resolution process for (R)- and (S)-1 production by diastereomeric salt formation using only one naturally-based resolving agent (S)-2 via a simple solvent switch method.^{5,6} However, the chiral discrimination mechanism of this phenomenon has not yet been clarified. In order to explain this mechanism, we investigated a wide range of practical solvents with ε values between 5 and 78, including both aprotic and protic solvents (Table 1). The absolute configurations of the resolved molecule changed sharply between ε values 27 and 29, and between 58 and 62. The resolution results were evaluated by the resolution efficiency (E), which was calculated as the product of the yield and diastereomer excess (% de) of the salt obtained.⁷ There proved to be a very interesting correlation between the diastereomeric excess (% de) and dielectric constant of the solvent used as shown in Figure 2. The salt mainly containing (S)-1 was obtained from the solvents having a relatively middle range of ε between 29 and 58, whereas the salt mainly containing (R)-1was obtained from the solvents with ε being lower than 27 or higher than 62. The configuration of the less-soluble diastereomeric salt crystallized in the resolution system depended on the ε of the solvent used. Elemental analysis revealed that the salts obtained from the solvent with ε between 29 and 58 contained one water molecule of crystallization per one salt. The salts obtained from the solvent with ε being lower than 27 or higher than 62, however, did not contain either water or solvent molecules in the crystal.^{5,6} These results suggest that the water molecule plays a very important role in the discrimination.

The crystal structures of the two salts, (S)-1·(S)-2·H₂O and (R)-1·(S)-2,⁸ were carefully studied in order to

ascertain the function of the water molecule during crystallization and the discrimination process. A part of the crystal structure of $(S)-1\cdot(S)-2\cdot H_2O$ is shown in Figure 3a. The water molecules are located between the layers of (S)-2 and (S)-1 molecules. The water molecule plays a role to bridge (S)-2 molecules and affords a space



Figure 2. Relationship between the diastereomeric excess of the lesssoluble diastereomeric salt and dielectric constant (ε) of the solvent used in the resolution.



Figure 3. Crystal structures of the less-soluble diastereomeric salts: (a) $(S)-1\cdot(S)-2\cdot H_2O$ salt; (b) $(R)-1\cdot(S)-2$ salt.

preferentially recognized by (S)-1 molecule. On the other hand in the crystal structure of (R)-1·(S)-2, (S)-2 molecules are not bridged by water molecules as shown in Figure 3b. For (S)-2, the molecules pack together exclusively by hydrophobic interactions between the phenyl rings. Due to this different crystal field the (S)-2 molecules adopt different conformations from those in the crystal of (S)-1·(S)-2·H₂O. This different crystal field should be more preferable for (R)-1 molecules to be recognized. These crystal structures indicate that if the ε value of the applied solvent is in the medium range, (S)-2, (R)-1 and (S)-1 molecules can be separated apart enough to accommodate a water molecule between them in the solution. The water molecule then plays a key role in making (S)-2 recognize (S)-1. If the ε value of the solvent used is lower than 27, (S)-2, (R)-1 and (S)-1 molecules should closely approach, meaning a water molecule cannot be accommodated between 1 and 2 molecules. Under these conditions the molecular recognition should be preferable for (S)-2 and (R)-1 molecules. Although suitable single crystals from a solvent with a higher ε value than 62 have not been obtained, elemental analysis confirmed only the anhydrous crystal can be obtained under these conditions. It can be assumed that in solvents with the high ε values, the interactions between (S)-2 molecules are governed by hydrophobic interactions between phenyl groups in a similar fashion as observed in low ε solvents. Therefore under high ε conditions, specific interactions between (S)-2 and (R)-1 should be favourable. The present results unequivocally demonstrate that the dielectric constant of the solvent employed in the resolution significantly affects the molecular discrimination process by controlling the molecular interactions involving the solvent molecules such as water.

Phenomena indicating chirality change by solvent used have been reported by Nohira et al. for the resolution of racemic phenylethylamine analogue (1-phenyl-2-(*p*tolyl)ethylamine)⁹ and benzothiazepin derivative (α -2-(*p*methoxyphenyl)-3-acetoxy-5-(β -dimethylaminoethyl)-2,3-dihydro-1, 5-benzothiazepin-4(5H)-one)¹⁰ with enantiopure mandelic acid as a resolving agent. To the best of our knowledge, however, the significant role of a dielectric constant of a solvent used in the resolution process has not been demonstrated before.

In conclusion, we found a very useful phenomenon that allowed us to control chiroselective molecular recognition in the resolution using only one chiral selector by simply changing the solvent. This finding will provide us with a new facile and effective resolution procedure, which if general could revolutionize the industrial process for isolating chiral molecules from racemic mixtures. In addition to its industrial significance, the present finding has clearly shown that the dielectric constant of the solvent can be used as one of the decisive factors on the chiroselective molecular recognition.

References and notes

- Jacques, J.; Collet, A.; Wilen, S. H. Enantiomers, Racemates, and Resolutions; Wiley-InterScience, 1981; p 251.
- 2. (*RS*)-1 was obtained from Ajinomoto Co., Inc. and used without any purification (containing 3.7% of water).
- (S)-2 was made of Yamakawa Chemical. White solid, >99.9% ee, CP 99.9%, mp 164.5°C (lit.: 161–163°C Kinugasa, N.; Harada, T.; Egusa, T.; Fujita, K.; Oku, A. Bull. Chem. Soc. Jpn. 1996, 3639; [α]_D²⁰ = +1.0 (c 4.0, MeOH) {lit.: [α]_D²⁰ +1.1 (c 4.0, MeOH)} Sakota, N.; Koine, N.; Okita, K. Nippon Kagaku Zasshi 1969, 90, 77; Chem. Abstr. 1968, 70, 115517.
- Sakurai, R.; Sakai, K.; Yuzawa, A.; Hirayama, N. Symposium Molecular Chirality 2003 (Oct. 19, Shizuoka), Abstract PA-11.
- 5. Sakai, K.; Sakurai, R.; Yuzawa, A.; Hatahira, K. Japan Patent Appl. 2003-338,118.
- 6. Sakai, K.; Sakurai, R.; Yuzawa, A.; Hirayama, N. *Tetrahedron: Asymmetry* **2003**, 3713–3718.
- 7. Resolution efficiency $(E, \%) = \text{yield } (\%) \times \text{diastereometric}$ excess $(\% \text{ de}) \times 0.02$.
- Crystallographic data for the structures of (S)-1·(S)-2·H₂O and (R)-1·(S)-2 have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 220041 and 220042, respectively. (S)-1·(S)-2·H₂O: A single colourless chip crystal of (S)-1·(S)-5·H₂O salt (0.40×0.07×0.04 mm) was grown from recrystallization conditions (MeOH) using recrystallized salt crystals (>99.9% de). X-ray intensities were measured up to

 $2\theta_{\text{max}} = 67.6^{\circ}$ with graphite monochromated Cu K_a radiation ($\lambda = 1.5419$) (Rigaku) at 293 K. C₂₂H₃₁N₃O₆S; Molecular weight 465.56; Monoclinic, P2₁ (# 4), a = 12.726(2), b = 5.3317(5), c = 17.901(2), $\beta = 100.395(4)$, V =1195.0(3), Z = 2, $D_{\text{calcd}} = 1.294$, R = 0.075; $R_{\text{w}} = 0.125$. Number of reflections measured = total 3912; Unique: 2555. (R)-1·(S)-2: A colourless platelet single crystal of (R)-1·(S)-5 salt ($0.40 \times 0.15 \times 0.03 \text{ mm}$) was grown from the recrystallization conditions (89% 2-propanol) using recrystallized salt crystals (>98.9% de). The X-ray intensities were measured up to $2\theta_{\text{max}} = 68.2^{\circ}$ with graphite monochromated Cu K_α radiation ($\lambda = 1.5419$) (Rigaku) at 293 K. C₂₂H₂₉N₃O₆S; Molecular weight 447.55; Monoclinic, P2₁ (# 4), a = 11.2302(4), b = 5.5390(2), c = 17.850(1), $\beta = 95.444(2)$, V = 1150.4(1), Z = 2, $D_{calcd} = 1.345$, R = 0.035, $R_w = 0.077$. Number of reflections measured = total 3851; Unique: 1561.

- Nohira, H.; Murata, H.; Asakura, I.; Terunuma, D. Japan Patent Kokai 59,110,656 (1984); *Chem. Abstr.* 1985, 102, 5896.
- 10. Nohira, H.; Nohira, M. Japan Patent Kokai 5,832,872 (1983); Chem. Abstr. 1983, 99, 70782.