ORGANIC LETTERS

2004
Vol. 6, No. 2
265−268

Toward Homogeneity of Chirality via Selective Formation of Homochiral or Heterochiral Aggregates

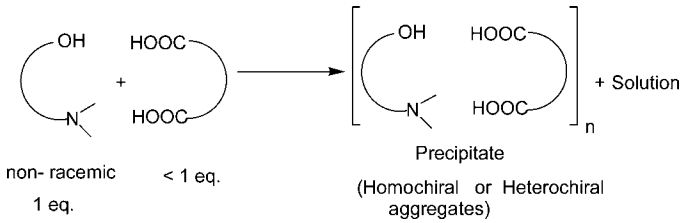
Mariappan Periasamy,* Sangarappan Sivakumar, Meda Narsi Reddy, and Meduri Padmaja

School of Chemistry, University of Hyderabad, Central University P. O., Hyderabad 500 046, India

mpsc@uohyd.ernet.in

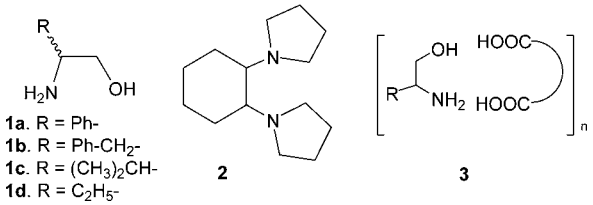
Received November 15, 2003

ABSTRACT



A new method of achieving homogeneity of chirality via purification of nonracemic (partially resolved) amino alcohols 1a–d and the C_2 chiral diamine 2 to obtain samples of higher ee, through preparation of homochiral and heterochiral aggregates using oxalic and fumaric acids, is described.

A method of achieving homogeneity of chirality via purification of nonracemic materials of lower enantiomeric purities has good synthetic potential, in addition to serving as a model for the evolution of homochirality in Nature under prebiotic conditions.[1] We wish to report here a new method of achieving homogeneity of chirality by purification of partially resolved (nonracemic) amino alcohols **1a**−**d**[2] and a C_2 chiral diamine **2**[3] via preparation of the corresponding hydrogen-bonded homochiral or heterochiral aggregates **3**, which may serve as a model for developing such methods for purification of nonracemic samples.



We have envisaged that if the formation of diastereomeric aggregates of the type **3** through hydrogen bonding could be induced using achiral spacers, it would result in the enhancement of enantiomeric excess. We have selected the partially resolved (nonracemic) 1,2-amino alcohols **1a**−**d** and the C_2 symmetric diamine **2** to examine this possibility. The nonracemic samples of amino alcohols **1** (15−90% ee) and diamine **2** (28−78% ee) were obtained by resolution of the corresponding racemic samples with dibenzoyl-L-tartaric acid. These samples, on treatment with oxalic acid or fumaric acid in acetone for 12 h at 25 °C, gave precipitate and filtrate fractions from which samples of higher enantiomeric excesses can be readily obtained. The results are summarized in Table 1.

When the nonracemic amino alcohols and the dicarboxylic acids are used in a 1:1 ratio, there is no enhancement of ee of samples obtained from the precipitate and filtrate fractions

(1) Feringa, B. L.; van Delden, R. A. *Angew. Chem., Int. Ed.* **1999**, *38*, 3418−3438.

(2) Prasad, A. S. B.; Kanth, J. V. B.; Periasamy, M. *Tetrahedron* **1992**, *48*, 4623−4628. The nonracemic amino alcohols **1a**−**1d** were prepared by the reduction of the corresponding oximes of the α-ketoesters using $NaBH_4$/I_2 reagent in THF.

(3) de Souza, S. E.; O'Brien, P.; Poumellec, P. *Tetrahedron:Asymmetry* **1997**, *8*, 2613−2618.

10.1021/ol036240b CCC: $27.50
Published on Web 12/19/2003

Table 1. Purification of Non-racemic Amino Alcohols **1** and Diamine **2** Using Oxalic Acid and Fumaric Acid[a]

			1 or **2** obtained from			
entry	substrate % ee	diacid (mmol)[b]	precipitate % ee[c]/conf	yield[d] (%)	filtrate % ee[c]/conf	yield[d] (%)
1	(*R*)-**1a**, 40	OA, 5.00	42 (*R*)	55	35 (*R*)	30
2	(*R*)-**1a**, 15	OA, 0.75	30 (*R*)	11	03 (*R*)	78
3	(*S*)-**1a**, 20	OA, 1.00	35 (*S*)	15	06 (*S*)	75
4	(*R*)-**1a**, 30	OA, 1.50	50 (*R*)	28	06 (*R*)	60
5	(*S*)-**1a**, 35	OA, 1.75	60 (*S*)	30	05 (*S*)	60
6	(*R*)-**1a**, 50	OA, 2.50	70 (*R*)	48	05 (*R*)	42
7	(*S*)-**1a**, 52	OA, 2.60	75 (*S*)	48	06 (*S*)	42
8	(*R*)-**1a**, 70	OA, 3.50	90 (*R*)	65	09 (*R*)	25
9	(*S*)-**1a**, 75	OA, 3.75	92 (*S*)	68	10 (*S*)	22
10	(*R*)-**1a**, 90	OA, 4.50	99 (*R*)	85	20 (*R*)	10
11	(*S*)-**1a**, 92	OA, 4.60	99 (*S*)	87	22 (*S*)	05
12	(*R*)-**1a**, 10	FA, 0.50	05 (*R*)	70	22 (*R*)	20
13	(*S*)-**1a**, 15	FA, 0.75	05 (*S*)	58	29 (*S*)	30
14	(*R*)-**1a**, 20	FA, 1.00	06 (*R*)	62	40 (*R*)	31
15	(*S*)-**1a**, 30	FA, 1.50	12 (*S*)	50	70 (*S*)	38
16	(*R*)-**1a**, 40	FA, 2.00	17 (*R*)	43	85 (*R*)	45
17	(*S*)-**1a**, 50	FA, 2.50	26 (*S*)	40	96 (*S*)	48
18	(*R*)-**1a**, 70	FA, 3.50	30 (*R*)	28	99 (*R*)	50
19	(*S*)-**1a**, 85	FA, 4.25	32 (*S*)	18	99 (*S*)	75
20	(*R*)-**1a**, 90	FA, 4.50	36 (*R*)	10	99 (*R*)	84
21	(*S*)-**1a**, 95	FA, 4.75	38 (*S*)	08	99 (*S*)	87
22	(*R*)-**1b**, 17	OA, 0.85	33 (*R*)	20	03 (*R*)	72
23	(*R*)-**1b**, 50	OA, 2.50	98 (*R*)	52	20 (*R*)	30
24	(*S*)-**1b**, 50	OA, 2.50	98 (*S*)	48	15 (*S*)	35
25	(*S*)-**1b**, 50	FA, 2.50	30 (*S*)	25	87 (*S*)	40
26	(*S*)-**1b**, 70	FA, 3.50	50 (*S*)	30	98 (*S*)	60
27	(*R*)-**1c**, 20	OA, 1.00	35 (*R*)	15	03 (*R*)	75
28	(*S*)-**1c**, 60	OA, 3.00	75 (*S*)	58	20 (*S*)	30
29	(*S*)-**1c**, 90	OA, 4.50	98 (*S*)	87	25 (*S*)	08
30	(*S*)-**1c**, 30	FA, 1.50	18 (*S*)	35	50 (*S*)	50
31	(*S*)-**1c**, 65	FA, 3.25	30 (*S*)	28	98 (*S*)	60
32	(*S*)-**1d**, 18	OA, 0.90	36 (*S*)	22	06 (*S*)	70
33	(*S*)-**1d**, 52	OA, 2.60	98 (*S*)	44	15 (*S*)	35
34	(*R*)-**1d**, 55	OA, 2.75	98 (*R*)	49	18 (*R*)	30
35	(*S*)-**1d**, 20	FA, 1.00	12 (*S*)	25	42 (*S*)	51
36	(*SS*)-**2**, 28	OA, 0.56	11 (*SS*)	17	37 (*SS*)	60
37	(*RR*)-**2**, 50	OA, 1.00	07 (*RR*)	13	64 (*RR*)	60
38	(*SS*)-**2**, 65	OA, 1.30	15 (*SS*)	14	79 (*SS*)	60
39	(*RR*)-**2**, 78	OA, 1.56	48 (*RR*)	28	91 (*RR*)	57
40	(*SS*)-**2**, 31	FA, 0.62	40 (*SS*)	30	21 (*SS*)	51
41	(*RR*)-**2**, 42	FA, 0.84	59 (*RR*)	47	23 (*RR*)	52
42	(*SS*)-**2**, 60	FA, 1.40	74 (*SS*)	68	19 (*SS*)	27
43	(*RR*)-**2**, 78	FA, 1.56	93 (*RR*)	60	33 (*RR*)	20
44	(*RR*)-**2**, 93	FA, 1.86	99 (*RR*)	75	40 (*RR*)	10

[a] The reactions were carried out using nonracemic amino alcohols (5 mmol) and dicarboxylic acid in acetone (60 mL) or nonracemic diamine (2 mmol) and diacid in acetone (5 mL); the contents were stirred at 25 °C for 12h. [b] OA = oxalic acid, FA = fumaric acid. [c] All ee values reported here are based on reported maximum[4a] $[\alpha]_D^{25} = +33$ (*c* 0.75, 1 N HCl) for (S)-**1a**, $[\alpha]_D^{25} = +23$ (*c* 1.2, 1 N HCl) for (R)-**1b**, $[\alpha]_D^{25} = +17$ (*c* 10, C_2H_5OH) for (S)-**1c**, $[\alpha]_D^{25} = +12.5$ (*c* 2, C_2H_5OH) for (*S*)-**1d** and maximum $[\alpha]_D^{25} = -31.85$ (*c* 0.5, 1 N HCl) obtained from >99% ee sample of (*R*,*R*)-**2** prepared following a reported procedure.[4b] [d] The yields are of the isolated products, based on the total amount of the starting nonracemic mixture used.

(entry no. 1 Table 1). However, interesting results were obtained when the dicarboxylic acids were used in smaller amounts, and optimum results were obtained using achiral diacid in 1:1 molar amounts equivalent to the % ee of the starting nonracemic samples (Table 1). These studies were also carried out using other solvents such as acetonitrile, methanol and THF. It was observed that acetone gave optimum results. In the case of the nonracemic amino alcohols **1a**−**d** using oxalic acid, the ee's of the samples obtained from the precipitate fraction were higher.

When using fumaric acid, the samples obtained from the filtrate fraction had higher ee's (Table 1). These results are in accordance with the precipitation of predominantly homochiral aggregates (*R*,*R* or *S*,*S*) in the case of oxalic acid and heterochiral aggregates (*R*,*S*,*R*,*S*) with fumaric acid. Opposite trends are observed in the runs using the C_2 symmetric diamine **2** (Table 1). Whereas the use of fumaric acid resulted in samples of higher ee's in the precipitate fraction, samples of higher ee's were obtained in the filtrate fraction in runs using oxalic acid. Enhancement of enantiomeric excesses through predominant formation of homo- or heterochiral aggregates reported here is further illustrated in the plots of ee's of starting materials verses ee's of samples obtained from precipitate and filtrate fractions (Figures 1 and 2) in the case of nonracemic **1a**. Similar trends were also observed for the data obtained with other derivatives (Table 1).

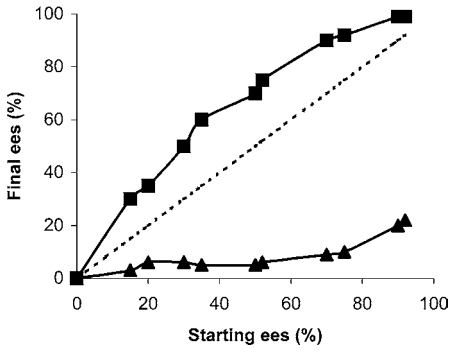


Figure 1. Purification of partially resolved **1a** using oxalic acid: (■) product obtained from precipitate fraction., (- - -) data points expected assuming no selectivity, (▲) products obtained from filtrate fractions.

The present method is different from previously reported cocrystallization techniques for the purification of certain nonracemic carboxylic acids,[5] because in these methods, the enantiomer present in excess invariably crystallizes out. In contrast, in the present method, the purification is due to selective formation of predominantly homo- or heterochiral aggregates in the precipitate fractions (Table 1 and Figures 1 and 2). This method is also different from the Horeau duplication[6] in which enhancement of ee's of the crystallized

(4) (a) Mckennon, M. J.; Meyers, A. I. *J. Org. Chem.* **1993**, *58*, 3568. (b) Corey, E. J.; Sarshar, S.; Azimioara, M. D.; Newbold, R. C.; Noe, M. C. *J. Am. Chem. Soc.* **1996**, *118*, 7851−7852.

(5) (a) Gabard, A.; Collet, A. *New J. Chem.* **1986**, *10*, 685−690. (b) Potter, G. A.; Garcia, C.; McCague, R.; Adger, B.; Collet, A, *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1666−1668.

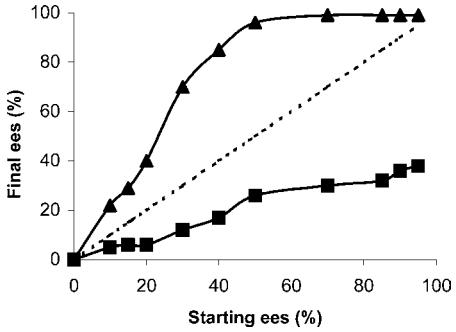


Figure 2. Purification of partially resolved **1a** using fumaric acid: (■) product obtained from precipitate fraction., (- - -) data points expected assuming no selectivity, (▲) products obtained from filtrate fractions.

samples is due to statistical distribution of dimers derived from the enantiomers present in the mixture without any selectivity.

The complexes obtained using nonracemic samples of **1a**−**d** did not yield crystals suitable for X-ray analysis. Fortunately, however, crystals suitable for X-ray analysis were obtained from the salt formed using racemic amino alcohol **1a** and fumaric acid (Figure 3).[7] The packing diagram

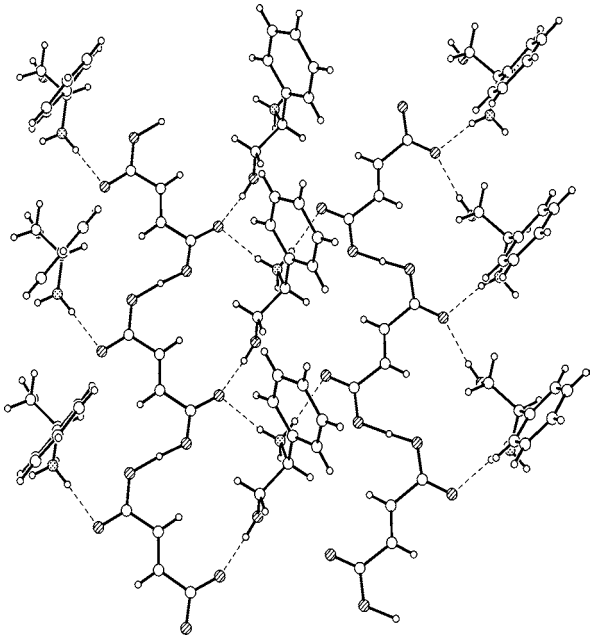


Figure 3. Crystal packing diagram of the complex of racemic phenylglycinol **1a** and fumaric acid.

showed layers of intermolecularly hydrogen-bonded monoanion of the acid alternating with layers of intermolecularly hydrogen-bonded amino alcohol moieties through N−H···O and O−H···O interactions, the closest contact distances being N−H···O═C (2.033 Å, carbonyl of the carboxylic acid moiety), N−H···O═C (2.019 Å, carbonyl of the carboxylate anion moiety), and O−H···O═C (1.924 Å, carbonyl of the carboxylate anion moiety). The alternate layers of amino alcohols are found to be heterochiral to each other.

In contrast, the crystal structure of the chiral diamine **2** and fumaric acid complex (Figure 4, entry 42 Table 1)

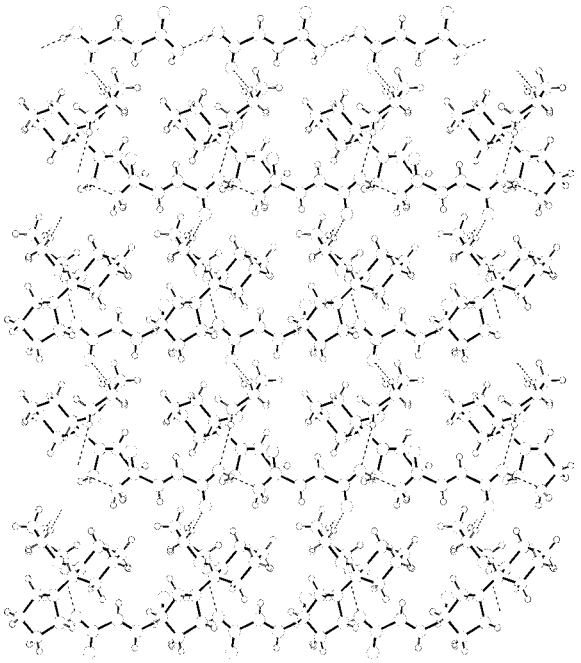


Figure 4. Crystal packing diagram of the complex of the diamine **2** and fumaric acid (entry 42, Table 1).

reveals that it is not a salt.[8] Here, the diamine moieties are placed between layers of the intermolecularly hydrogen-bonded fumaric acid through three types of C−H···O interactions, the shortest (2.48 Å) being the hydrogen bond between the C−H α to the nitrogen and the oxygen atom of the carbonyl group of the fumaric acid moiety.

Presumably, the enantiomer present in excess in these cases forms hydrogen-bonded complexes with the achiral dicarboxylic acid spacer, and the selective packing to obtain homochiral aggregates (*R*,*R*,*R*) or heterochiral aggregates (*R*,*S*,*R*,*S*) dictates the precipitation of homochiral or heterochiral aggregates from the solution.

(6) (a) Vigneron, J. P.; Dhaenens, M.; Horeau, A. *Tetrahedron* **1973**, *29*, 1055−1059. (b) Fleming, I.; Ghosh, S. K. *J. Chem. Soc., Chem. Commun*. **1994**, 99−100.

(7) **Crystal Data.** Complex of the racemic phenylglycinol **1a** and fumaric acid $C_{12}H_{15}NO_5$, MW = 253.25, monoclinic, space group *P*21 /*n*, *a* = 12.816(3) Å, *b* = 6.3361(13) Å, *c* = 16.493(3) Å, *β* = 105.78(3)°, *V* = 1288.6(5) Å^3, *Z* = 4, ρ_c = 1.305 mg m^{-3}, μ = 0.102 mm^{-1}, *T* = 293 K. Of the 3097 reflections collected, 3097 were unique (R_{int} = 0.0000). Refinement on all data coverged at R_1 = 0.0596, wR_2 = 0.1709 (see Supporting Information).

(8) **Crystal Data.** Complex of the diamine **2** and fumaric acid, $C_{18}H_{30}N_2O_4$, MW = 338.44, monoclinic, space group *p*_21, *a* = 7.792(4) Å, *b* = 15.115(13) Å, *c* = 8.009(9) Å, *β* = 98.12(6)°, *V* = 933.9(14) Å^3, *Z* = 2, ρ_c = 1.204 mg m^{-3}, μ = 0.085 mm^{-1}, *T* = 298 K. Of the 2812 reflections collected, 2801 were unique (R_{int} = 0.0000). Refinement on all data coverged at R_1 = 0.0549, wR_2 = 0.1323 (see Supporting Information).

Previously, Saigo and co-workers[9] reported crystal structures of a series of salts obtained using chiral or racemic samples of some monoamines with certain achiral monocarboxylic acids, which revealed the formation of hydrogen-bonded aggregates. However, these authors did not include the chiral diamines or achiral dicarboxylic acids in their studies since entropy effects would be different in these cases. Unfortunately, in this study the nature of complexes obtained using nonracemic samples of monoamines with achiral carboxylic acids was not examined. However, perusal of the results reported by these authors and the observation of selective formation of homochiral or heterochiral aggregates from nonracemic amino alcohols and diamines described here would suggest that the phenomena observed may be more general in nature, and hence further studies on crystal engineering using nonracemic samples of monoamines, diamines, and amino alcohols with mono- and dicarboxylic acids should lead to fruitful results.

(9) Kinbara, K.; Hashimoto, Y.; Sukegawa, M.; Nohira, H.; Saigo, K. *J. Am. Chem. Soc.* **1996**, *118*, 3441−3449. We thank one of the referees for bringing this paper to our attention.

The chiral 1,2-amino alcohols and diamines have a wide range of applications in asymmetric synthesis, as well as in the synthesis of pharmaceuticals.[10] Accordingly, the methods of purification of nonracemic amino alcohols and diamines using inexpensive achiral reagents described here should find applications in large-scale synthetic operations to purify partially resolved chiral compounds.

Acknowledgment. We are thankful to the DST, CSIR and UGC (New Delhi) for financial support and research fellowships. Support of the UGC under the University of Potential for Excellence Program is also gratefully acknowledged.

Supporting Information Available: X-ray crystal data for the complexes of the amino alcohol **1a** and diamine **2** with fumaric acid in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

OL036240B

(10) (a) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835−875. (b) Periasamy, M.; Kumar, N. S.; Kumar, S. S.; Dharma Rao, V.; Ramanathan, C. R.; Venkatraman, L. *J. Org. Chem.* **2001**, *66*, 3828−3833.