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Stereocontrol of molecular jump-rope: crystallization-induced asymmetric transformation of planar-chiral cyclophanes

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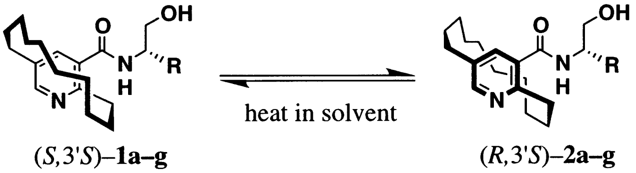
Abstract—Stereocontrol of cyclophane-type planar chirality was achieved by spontaneous dynamic resolution via crystallization-induced asymmetric transformation. Simply heating a 1/1 mixture of the solid and the liquid diastereoisomers of bridged nicotinamides (*S*,3′*S*)-**1a**–**f** and (*R*,3′*S*)-**2a**–**f** accelerated their rope-skipping isomerization with precipitation of the solid (*S*,3′*S*)-**1a**–**f**, completing the disequilibriation to (*S*,3′*S*)-**1a**–**f** with up to 99% *de*. © 2001 Elsevier Science Ltd. All rights reserved.

Spontaneous dynamic resolution with acidic or basic catalysts is a well-established method for asymmetric disequilibriation, namely, as crystallization-induced asymmetric transformation.[1–3] However, only limited examples have been known of '*self-controlled*' resolution without any external reagents or catalysts to produce homochiral enantiomers[4,5] or diastereoisomers.[6,7] In particular, thermodynamic control of the C–C single bond of atropisomers is apparently a more difficult target because it often requires conformational disequilibriation between energetically close stereoisomers. Recently, much attention has been paid to planar-chiral molecules such as chiral cyclophanes or metal–π complexes as biomimetic asymmetric reagents[8–10] or chiral nucleophilic catalysts.[11] Though the dynamic resolution of axially chiral molecules has been reported previously,[5,7] the stereochemistry of planar chirality has not yet been controlled nor the rope-skipping dynamics in cyclophane molecules.[12] In relation to our recent studies of highly enantioselective reduction with bridged NADH analogs,[8] we have been studying the stereocontrol of their planar-chiral precursors, namely, pyridinophanes **1** and **2**. This communication describes the first stereocontrol of molecular jump-rope (or skipping-rope) via crystallization-induced asymmetric transformation in a molten state to give a series of solid pyridinophanes, (*S*,3′*S*)-**1a**–**f**, over the corresponding liquid diastereoisomers, (*R*,3′*S*)-**2a**–**f**.



a: R = *i*–Pr; **b**: R = Bn; **c**: R = *t*–Bu; **d**: R = *i*–Bu; **e**: R =Et; **f**: R = Ph; **g**: R = Me

Stereocontrol of (*S*,3′*S*)-**1a** and (*R*,3′*S*)-**2a** enriching the desirable planar chirality inevitably requires the net directional skipping motion of their oligomethylene jump-rope. However, the thermodynamic stabilities of the two diastereoisomers are almost identical, so that their populations did not change significantly on heating a solution of their 1/1 mixture. To accumulate single planar chirality, we focused on the differences in their physical properties between (*S*,3′*S*)-**1a** and (*R*,3′*S*)-**2a**, which are solid and liquid isomers, respectively. Heating a concentrated liquid sample of their 1/1 mixture in a recovery flask[13] caused spontaneous dynamic resolution with significant enrichment of (*S*)-planar chirality to give the solid (*S*,3′*S*)-**1a** over the liquid (*R*,3′*S*)-**2a**. Table 1 summarizes the efficiency of the stereocontrol at various temperatures. Although no significant change was observed at 70°C (5% *de*, entry 1), more efficient stereocontrol became evident at higher temperatures, and the diastereomeric excess of (*S*,3′*S*)-**1a** reached 44% *de* and 83% *de* at 90 and 110°C, respectively (entries 2 and 3). A further increase in the heating temperature diminished the efficiency somewhat to give 61% *de* and −5% *de* [the latter giving (*R*,3′*S*)-**2a** predominantly] at 130 and 150°C, respectively (entries 4 and 5). The following two factors describe the kinetic

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Keywords: stereocontrol; planar chirality; cyclophanes; rope-skipping isomerization; crystallization-induced asymmetric transformation.

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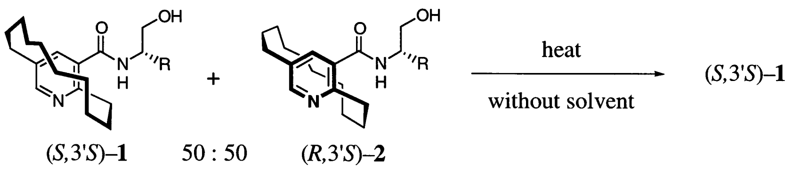

Table 1. Crystallization-induced asymmetric transformation from (*R*,3′*S*)-**2** into (*S*,3′*S*)-**1**[a]

Entry	**1**, **2**	Mp (°C)		Conditions		Final ratio[b]	
		(*S*,3′*S*)-**1**	(*R*,3′*S*)-**2**	*T* (°C)	*T*	Config.	De (%)
1	**a**	160–161	Oil	70	24 h	(*S*,3′*S*)-**1a**	5
2	**a**	160–161	Oil	90	24 h	(*S*,3′*S*)-**1a**	44
3	**a**	160–161	Oil	110	24 h	(*S*,3′*S*)-**1a**	83
4	**a**	160–161	Oil	130	24 h	(*S*,3′*S*)-**1a**	61
5	**a**	160–161	Oil	150	24 h	(*R*,3′*S*)-**2a**	−5[c]
6	**a**	160–161	Oil	90	4 d	(*S*,3′*S*)-**1a**	91
7	**a**	160–161	Oil	110	3 d	(*S*,3′*S*)-**1a**	96
8	**b**	178–179	Oil	110	4 d	(*S*,3′*S*)-**1b**	99
9	**c**	170–171	Oil	110	5 d	(*S*,3′*S*)-**1c**	95
10	**d**	162–163	Oil	110	5 d	(*S*,3′*S*)-**1d**	98
11	**e**	158–159	Oil	110	4 d	(*S*,3′*S*)-**1e**	90
12	**f**	170–171	139–140	110	24 h	(*R*,3′*S*)-**2f**	−7[c]
13	**f**	170–171	139–140	90	6 d	(*S*,3′*S*)-**1f**	40
14	**g**	Oil	Oil	110	24 h	(*S*,3′*S*)-**1g**	0.7[c]

[a] The isomerization started with a 1/1 mixture (ca. 20 mg) of **1** and **2**.

[b] A minus sign indicates the predominant formation of (*R*,3′*S*)-**2**. Configuration and the ratio were determined by HPLC by using SenshuPak Silica-3301-N column.

[c] Solid portion was not precipitated.

behavior: (1) isomerization between (*S*,3′*S*)-**1a** and (*R*,3′*S*)-**2a** by 'rope-skipping' motion and (2) net growth of crystalline (*S*,3′*S*)-**1a** which is '*dissolved*' in the liquid (*R*,3′*S*)-**2a**. These rates are expected to show the opposite behavior as the temperature increases; the rope-skipping becomes faster[8,14] and the crystal growth seems to become slower since the latter is the general behavior under supercooling conditions near melting points.[15] Thus, the rate-determining step shifts from the one to the other at some point, which best rationalizes the optimal temperature for the efficiency. The diastereomeric excess of (*S*,3′*S*)-**1a** eventually reached 91% *de* and 96% *de* at 90 and 110°C, respectively, simply by prolonging the reaction time to several days (entries 6 and 7).

Fig. 1 depicts the X-ray structure around a unit cell of the crystalline (*S*,3′*S*)-**1a**.[16] There are two types of intermolecular hydrogen bonds: one is between N–$\underline{H}$ and C=$\underline{O}$ of the carbamoyl groups, and the other is between O–$\underline{H}$ and a pyridine nitrogen. In particular, the configuration of the asymmetric carbon in (*S*,3′*S*)-**1a** seems to strongly affect the geometry of the hydroxy group as regards the latter type of hydrogen bonds, so that it should play an important role in determining their physical states.

Similarly, compounds (*S*,3′*S*)-**1b**–**e** and (*R*,3′*S*)-**2b**–**e** also have solid and liquid states at room temperature, respectively. Heating a 1/1 mixture of (*S*,3′*S*)-**1b**–**e** and (*R*,3′*S*)-**2b**–**e** at 110°C also shifted their rope-skipping equilibria to their solid sides with the diastereomeric excesses of (*S*,3′*S*)-**1b**–**e** reaching 90–99% *de* after 3–5 days (entries 8–11). For compounds (*S*,3′*S*)-**1f** and (*R*,3′*S*)-**2f**, the diastereoisomers of which are both solids, nothing significant was observed upon heating at 110°C because the mixture kept melting and did not show the appearance of any solids (entry 12). However, a slow but steady disequilibriation proceeded at 90°C, and the ratio of (*S*,3′*S*)-**1f** and (*R*,3′*S*)-**2f** finally reached 70/30 (40% *de*) after 6 days (entry 13).

On the contrary, neither (*S*,3′*S*)-**1g** and (*R*,3′*S*)-**2g**, which are both liquids (entry 14) nor (*S*,3′*S*)-**1a-f** in solution exhibited similar disequilibriation, and, therefore, the preferential formation of (*S*,3′*S*)-**1a**–**e** is ascribed to crystallization-induced asymmetric transformation in the molten state: the energy differences due

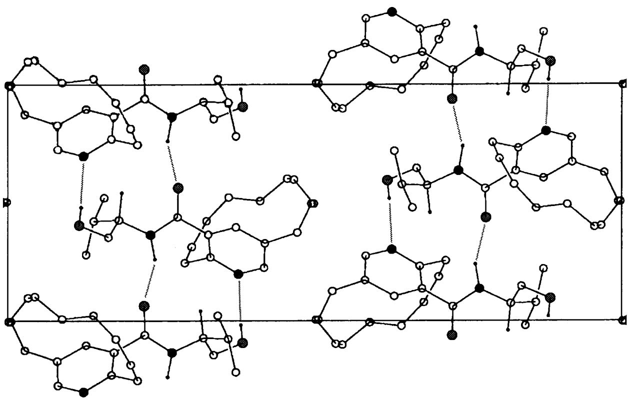

Figure 1. X-Ray crystallographic structure of (*S*,3′*S*)-**1a** in a unit cell showing intermolecular hydrogen bonds of **1a**.

Table 2. Selected physical data for (*S*,3′*S*)-**1a**–**g** and (*R*,3′*S*)-**2a**–**g**

Compounds		CD spectral data (λ_{ext})[a]	Specific rotation[b]
(*S*,3′*S*)-**1**	**a**	282 ($\Delta\varepsilon$ +10.6), 259 (−0.2), 226 (+18.0)	Ref. 8
	b	282 ($\Delta\varepsilon$ +9.0), 259 (−0.2), 228 (+14.8)	$[\alpha]_D^{21}=+62.3$ ($c=1$)
	c	282 ($\Delta\varepsilon$ +11.4), 260 (−0.6), 227 (+20.2)	$[\alpha]_D^{22}=+66.6$ ($c=1$)
	d	281 ($\Delta\varepsilon$ +12.0), 259 (−0.2), 226 (+19.7)	$[\alpha]_D^{21}=+65.3$ ($c=1$)
	e	282 ($\Delta\varepsilon$ +10.2), 259 (−0.2), 226 (−16.4)	$[\alpha]_D^{22}=+68.3$ ($c=1$)
	f	284 ($\Delta\varepsilon$ +10.5), 260 (−1.2), 226 (+24.2)	$[\alpha]_D^{20}=+63.2$ ($c=1$)
	g	283 ($\Delta\varepsilon$ +10.6), 258 (−0.2), 228 (+17.5)	$[\alpha]_D^{26}=+82.2$ ($c=1$)
(*R*,3′*S*)-**2**	**a**	282 ($\Delta\varepsilon$ −10.0), 259 (+0.8), 221 (−15.6)	Ref. 8
	b	282 ($\Delta\varepsilon$ −10.0), 259 (+0.8), 221 (−15.6)	$[\alpha]_D^{24}=-106.4$ ($c=1$)
	c	282 ($\Delta\varepsilon$ −10.9), 259 (+1.6), 224 (−19.0)	$[\alpha]_D^{22}=-73.0$ ($c=1$)
	d	283 ($\Delta\varepsilon$ −12.2), 259 (+1.6), 226 (−23.0)	$[\alpha]_D^{23}=-98.0$ ($c=0.87$)
	e	282 ($\Delta\varepsilon$ −11.4), 259 (+0.8), 225 (−19.4)	$[\alpha]_D^{22}=-95.6$ ($c=1$)
	f	283 ($\Delta\varepsilon$ −12.6), 259 (+0.0), 228 (−14.8)	$[\alpha]_D^{20}=-62.7$ ($c=1$)
	g	282 ($\Delta\varepsilon$ −9.8), 259 (+0.7), 225 (−17.6)	$[\alpha]_D^{25}=-87.9$ ($c=1$)

[a] Measured in acetonitrile.

[b] Measured in chloroform.

to the heat of fusion shift the whole equilibria to the side of (*S*,3′*S*)-**1a**–**e** with a single planar-chiral moiety. The optimized diastereomeric excesses of (*S*,3′*S*)-**1a**–**e** are mostly in increasing order according to their increasingly higher melting points (except for **1c**) (entries 7–11). In the case of **1f** and **2f**, a moderate diastereomeric excess resulted from the relatively small difference in the melting points, which is still effective to disequilibriate the two solid isomers.

The absolute configurations of (*S*,3′*S*)-**1b**–**g** were unequivocally determined by comparing their R_f values and/or retention times in HPLC with the authentic samples derived from (*S*)-bridged nicotinic acid.[8b] The CD spectral data and specific rotations of (*S*,3′*S*)-**1** and (*R*,3′*S*)-**2** are summarized in Table 2. As shown in Fig. 2, those CD spectra are so characteristic as to exhibit either two positive or two negative Cotton effects (221–228 and 281–284 nm) and are mostly dependent on their planar chirality. These results indicate that the CD spectra are remarkably useful for assigning the absolute configuration to these types of chiral cyclophanes.

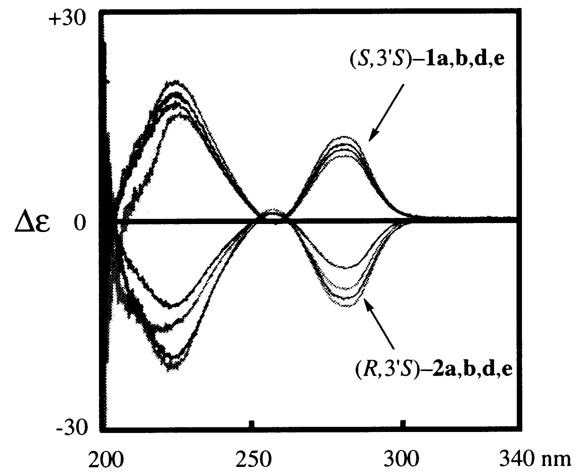

Figure 2. CD spectra of (*S*,3′*S*)-**1a**,**b**,**d**,**e** and (*R*,3′*S*)-**2a**,**b**,**d**,**e**.

Consequently, stereocontrol of the molecular jump-rope was accomplished between the bridged nicotinamide diastereoisomers (*S*,3′*S*)-**1a**–**f** and (*R*,3′*S*)-**2a**–**f** with significant enrichment of the single planar-chiral moieties simply upon heating their 1/1 mixture. Our previous method of enriching either one of their diastereoisomers has required a couple of repeated processes: alternate separation of the desirable planar chirality and erasure of the undesirable chirality via random rope-skipping isomerization upon heating in solution.[8] The present dynamic resolution based on crystallization-induced asymmetric transformation could provide an efficient and potentially versatile method for synthesizing homochiral cyclophane molecules with high functionality.

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