ORGANIC LETTERS

2005
Vol. 7, No. 9
1797−1800

Spontaneous Racemization and Epimerization Behavior in Solution of Chiral Nitroxides

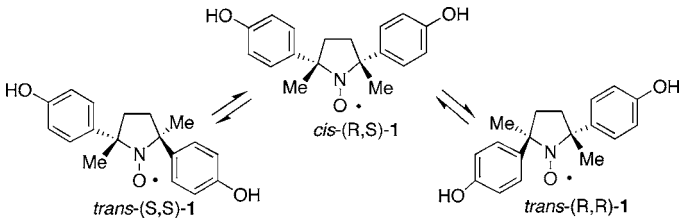
Naohiko Ikuma,[†,‡] Hirohito Tsue,[†,‡] Naoko Tsue,[‡] Satoshi Shimono,[‡] Yoshiaki Uchida,[‡] Kazuyoshi Masaki,[‡] Nagahisa Matsuoka,[‡] and Rui Tamura*[,†,‡]

Graduate School of Global Environmental Studies and Graduate School of Human and Environmental Studies, Kyoto University, Kyoto 606-8501, Japan

tamura-r@mbox.kudpc.kyoto-u.ac.jp

Received February 24, 2005

ABSTRACT



Enantiomerically enriched samples of chiral cyclic nitroxides with a 4-hydroxyphenyl group on the stereogenic center bearing the NO radical group undergo unprecedented spontaneous racemization and/or epimerization in aprotic solvents, which can be well accounted for by the multistep equilibrations involving planar quinoid intermediates.

Recently, we have successfully prepared all-organic paramagnetic liquid crystals that contain a chiral five-membered cyclic nitroxide unit (*trans*-**1**) within the rigid core and show nematic and chiral-nematic (cholesteric) phases.[1] During this synthetic study,[2,3] we have noticed that the optical rotations of the enantiomerically enriched *trans*-**1**, **2**, and *trans*-**3** gradually decrease in aprotic solvents. Furthermore, HPLC analytical studies using a chiral stationary phase column[4] to determine their ee and/or de values have indicated the occurrence of spontaneous racemization for **2**, epimerization for *trans*-**3**, and both racemization and epimerization for *trans*-**1**.

Although a certain chiral nitroxide was reported to racemize under oxidizing conditions,[5] there has been no precedent for such spontaneous racemization and epimerization in solution. Therefore, to clarify the mechanism of this unexpected racemization and epimerization and to find a way to prevent them, we investigated the effects of the solvent, the solute concentration, the temperature, and the light irradiation on the racemization and epimerization, together with the kinetics of the racemization in solution.

When a $CHCl_3$ solution (45.0 mM) of (*S*)-enriched **2** of 42% ee was kept standing at 20 °C, the ee value of **2** in solution decreased gradually to give an almost racemic solution after one month, indicating the occurrence of spontaneous racemization in solution. The racemization

[†] Graduate School of Global Environmental Studies.
[‡] Graduate School of Human and Environmenetal Studies.

(1) Ikuma, N.; Tamura, R.; Shimono, S.; Kawame, N.; Tamada, O.; Sakai, N.; Yamauchi, J.; Yamauchi, Y. *Angew. Chem., Int. Ed.* **2004**, *43*, 3677−3682.

(2) Ikuma, N.; Tamura, R.; Shimono, S.; Kawame, N.; Tamada, O.; Sakai, N.; Yamauchi, J.; Yamauchi, Y. *Mendeleev Commun.* **2003**, 109−111.

(3) Shimono, S.; Tamura, R.; Ikuma, N.; Takahashi, H.; Sakai, N.; Yamauchji, J. *Chem. Lett.* **2004**, *33*, 932−933

(4) HPLC analysis was carried out by using a chiral stationary phase column (Daicel Chiralcel OD-H, 0.46 × 25 cm), a mixture of hexane and 2-PrOH (9:1) as the mobile phase at a flow rate of 0.5 or 1.0 mL min^{-1}, and a UV−vis spectrometer (254 nm) as the detector.

(5) Rychnovsky, S. D.; Beauchamp, T.; Vaidyanathan, R.; Kwan, T. *J. Org. Chem.* **1998**, *63*, 6363−6374.

10.1021/ol050401p CCC: $30.25
Published on Web 03/26/2005

occurred gradually in aprotic solvents such as benzene, $CHCl_3$, and CH_2Cl_2 at 25 °C (Figure 1) and was accelerated

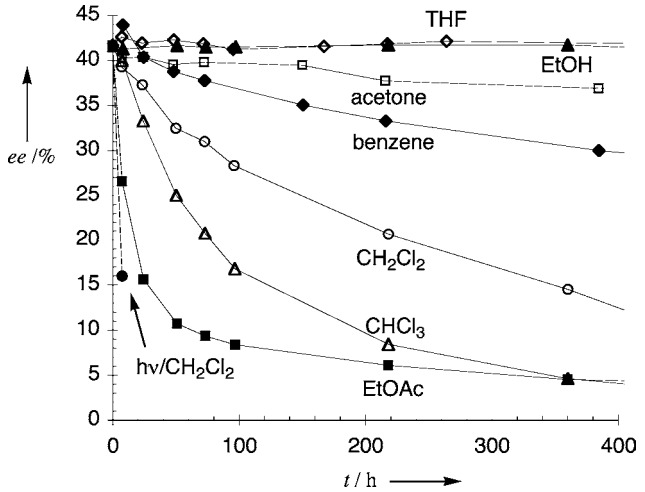
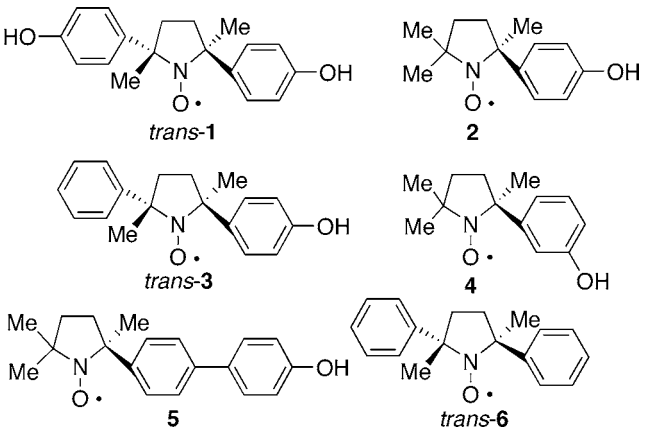


Figure 1. Racemization of (*S*)-rich **2** (42% ee) in various solvents at a concentration of 45.0 mM except for in benzene (9.0 mM).

by increasing the solute concentration. In particular, racemization proceeded promptly in EtOAc or was dramatically accelerated by irradiating with a 27 W fluorescent lamp in CH_2Cl_2 at 25 °C, implying a radical mechanism. In contrast, racemization was greatly suppressed in protic solvents or hydrogen-bonding acceptor solvents such as EtOH or THF (Figure 1), respectively, or at low temperatures such as −20 °C even in CH_2Cl_2.



Likewise, both *trans*-(2*S*,5*S*)-**3** of 96% ee and *trans*-(±)-**3** underwent partial epimerization gradually only at the C(2) position bearing 4-hydroxyphenyl group in CH_2Cl_2 and promptly in EtOAc to give partly *cis*-(2*R*,5*S*)-**3** and *cis*-(±)-**3**, respectively, according to the equilibrium constant (trans/cis 67:33).

For *trans*-(2*S*,5*S*)-**1** of 97% ee, both spontaneous epimerization and racemization were observed in EtOAc, while no change was noted in EtOH (Figure 2).

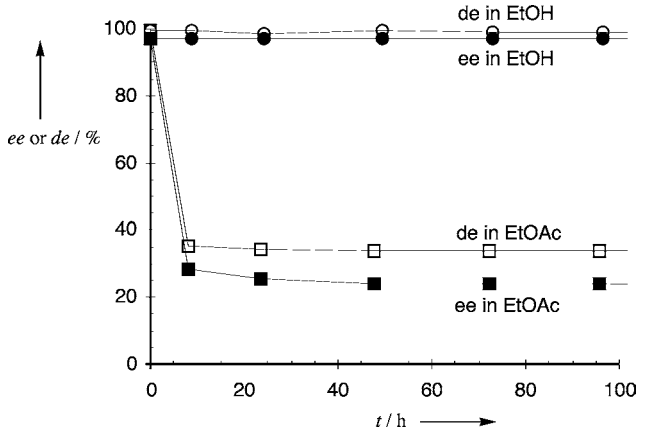


Figure 2. Epimerization and racemization of *trans*-(2*S*,5*S*)-**1** in EtOAc (16.1 mM) but not in EtOH (32.2 mM).

To decide whether such spontaneous racemization and epimerization occur intra- or intermolecularly, we have measured the number-averaged molecular weights of (±)-**2** and *trans*-(±)-**3** in $CHCl_3$ over a range of concentrations from 5.0 to 40.0 mM at 35 °C by using a vapor pressure osmometer and compared these data with those of nonphenolic *trans*-(±)-**6** (Table 1).[6] As a result, at concentrations

Table 1. Number-Averaged Molecular Weight (NMW) of (±)-**2**, *trans*-(±)-**3**, and *trans*-(±)-**6** Determined at 35 °C by Vapor Pressure Osmometer[a]

compound	concn (mM)	NMW	NMW/FW[b]	monomer/dimer[c]
(±)-**2**	5.0	250	1.14	6.1
	10.0	300	1.36	1.8
	20.0	305	1.38	1.6
	40.0	302	1.37	1.7
trans-(±)-**3**	6.0	281	1.00	
	12.0	382	1.35	1.9
trans-(±)-**6**	12.0	256	0.96	
	24.0	268	1.00	

[a] Molecular weights were measured in $CHCl_3$ using benzil as the standard sample for calibration, and the results of the triplicate experiments were reproducible. [b] FW: formula weight. [c] Ratio.

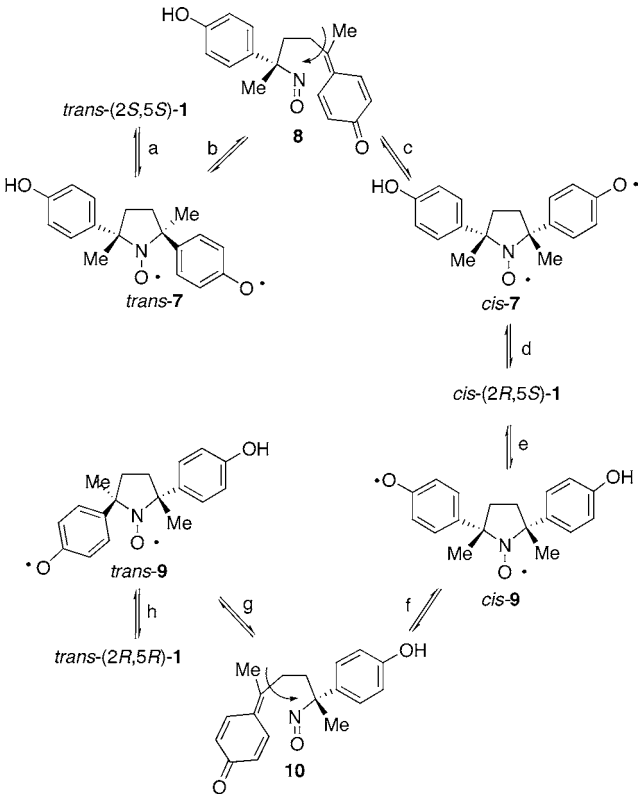
greater than 10.0 mM, where racemization and epimerization occur appreciably, molecular association was noted for (±)-**2** and *trans*-(±)-**3** showing coexistence of the monomer and the dimer in $CHCl_3$, whereas no aggregation was observed for *trans*-(±)-**6** over the same concentration range, indicating an intermolecular origin of the spontaneous racemization and epimerization and the participation of the OH group. It is quite plausible that the dimer structure is formed by the

(6) (a) Einhorn, J.; Einhorn, C.; Ratajczak, F.; Gautier-Luneau, I.; Pierre, J.-L. *J. Org. Chem.* **1997**, *62*, 9385−9388. (b) Benfaremo, N.; Steenbock, M.; Klapper, M.; Müllen, K.; Enkelmann, V.; Cabrera, K. *Liebigs Ann. Chem.* **1996**, 1413−1415.

hydrogen bond between the OH and the NO radical groups in solution as well as in the crystalline state.[2,7]

To gain more insight into the mechanism of the racemization and epimerization, we have synthesized phenolic nitroxides (*S*)-**4** (89% ee) and (*S*)-**5** (87% ee), which are the *m*-hydroxy analogue and the biphenyl homologue of (*S*)-**2**, respectively. These optically active nitroxides as well as *trans*-(2*S*,5*S*)-**6** did not undergo spontaneous racemization at all in solution. Furthermore, bis(*p*-alkoxy) analogues of *trans*-(2*S*,5*S*)-**1** showed neither epimerization nor racemization in solution.[1] These results strongly suggest the participation of a planar quinoid intermediate, which is known as the cause of racemization for a few chiral closed-shell molecules,[8] in both racemization and epimerization processes. Namely, the mechanism of epimerization of *trans*-(2*S*,5*S*)-**1** can be accounted for in terms of the multistep equilibrations involving (a) intermolecular abstraction of a phenolic hydrogen atom by the neighboring NO radical to generate the phenoxy radical *trans*-**7** and the corresponding hydroxylamine, (b) formation of the planar quinoid intermediate **8**, (c) free rotation of the quinoid moiety in **8** and the subsequent intramolecular regeneration of the C−N bond to give *cis*-**7**, and (d) intermolecular hydrogen abstraction by the phenoxy radical of *cis*-**7** from the resulting hydroxylamine or another hydroxy group to give meso *cis*-(2*R*,5*S*)-**1** (Scheme 1).

Scheme 1. Mechanism of Epimerization and Racemization of *trans*-(2S,5S)-**1**[a]

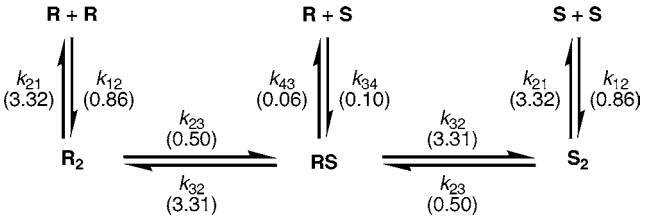


[a] See the text for the details of processes a−h.

Additional multistep equilibrations involving (e) formation of the other phenoxy radical (*cis*-**9**), (f) formation of the quinoid intermediate (**10**), (g) intermolecular recombination to give *trans*-**9**, and (h) intermolecular hydrogen abstraction to give *trans*-(2*R*,5*R*)-**1** can effectively explain the mechanism of this eventual racemization of *trans*-(2*S*,5*S*)-**1**.

The kinetics of racemization of (*S*)-rich **2** of 85% ee in $CHCl_3$ (20.0 mM) at 20 °C was solved numerically by using a laboratory-made program that implemented a fourth-order Runge−Kutta algorithm.[9] Because, as mentioned above, the observed spontaneous racemization is initiated by intermolecular association of nitroxides, five generic species that can interconvert would be involved in the present racemization, as shown in Scheme 2. **R** and **S** represent the

Scheme 2. Racemization Pathway of **2**[a]



$$-\frac{d[\mathbf{R}]}{dt} = k_{12}[\mathbf{R}]^2 - k_{21}[\mathbf{R}_2] + k_{34}[\mathbf{R}][\mathbf{S}] - k_{43}[\mathbf{RS}]$$

$$-\frac{d[\mathbf{S}]}{dt} = k_{12}[\mathbf{S}]^2 - k_{21}[\mathbf{S}_2] + k_{34}[\mathbf{R}][\mathbf{S}] - k_{43}[\mathbf{RS}]$$

$$-\frac{d[\mathbf{R}_2]}{dt} = -k_{12}[\mathbf{R}]^2 + k_{21}[\mathbf{R}_2] + k_{23}[\mathbf{R}_2] - k_{32}[\mathbf{RS}]$$

$$-\frac{d[\mathbf{S}_2]}{dt} = -k_{12}[\mathbf{S}]^2 + k_{21}[\mathbf{S}_2] + k_{23}[\mathbf{S}_2] - k_{32}[\mathbf{RS}]$$

$$-\frac{d[\mathbf{RS}]}{dt} = -k_{34}[\mathbf{R}][\mathbf{S}] + k_{43}[\mathbf{RS}] - k_{23}[\mathbf{R}_2] - k_{23}[\mathbf{S}_2] + 2k_{32}[\mathbf{RS}]$$

[a] Values in parentheses represent the rate constants (10^{-3} mol L^{-1} sec^{-1}).

monomeric (*R*)- and (*S*)-enantiomers, respectively. $\mathbf{R}_2$ and $\mathbf{S}_2$ indicate the homodimers of (*R*)- and (*S*)-enantiomers, respectively, and **RS** designates their heterodimer. Use of the program allows systems of linked differential equations, which are formulated by a combination of the five concentration terms and the six rate constants, to be solved simultaneously to analyze the concentrations of the five species as a function of time (Figure 3). The program

(7) (a) Reznikov, V. A.; Volodarskii, L. B. *Russ. Chem. Bull.* **1996**, *45*, 384−392. (b) Reznikov, V. A.; Burchak, O. N.; Vishnivetskaya, L. A.; Volodarsky, L. B.; Rybalova, T. V.; Gatilov, Yu. V. *Russ. J. Org. Chem.* **1997**, *33*, 1302−1310. (c) Kotake, Y.; Kuwata, K.; Janzen, E. G. *J. Phys. Chem.* **1979**, *83*, 3024−3029. (d) Chiarelli, R.; Rassat, A.; Rey, P. *Chem. Commun.* **1992**, 1081−1082. (e) Ahrens, B.; Davidson, M. G.; Forsyth, V. T.; Mahon, M. F.; Johnson, A. L.; Mason, S. A.; Price, R. D.; Raithby, P. R. *J. Am. Chem. Soc.* **2001**, *123*, 9164−9165.

(8) (a) Matsuo, K.; Yamamoto, Y.; Kado, N.; Yamazaki, M.; Nagata, O.; Kata, H.; Tsuji, A. *Chem. Pharm. Bull.* **2001**, *49*, 101−104. (b) Venter, D. P. *Tetrahedron* **1991**, *47*, 5019−5024.

(9) Jurs, P. C. *Computer Software Applications in Chemistry*, 2nd ed.; Wiley & Sons: New York, 1996; pp 78−103.

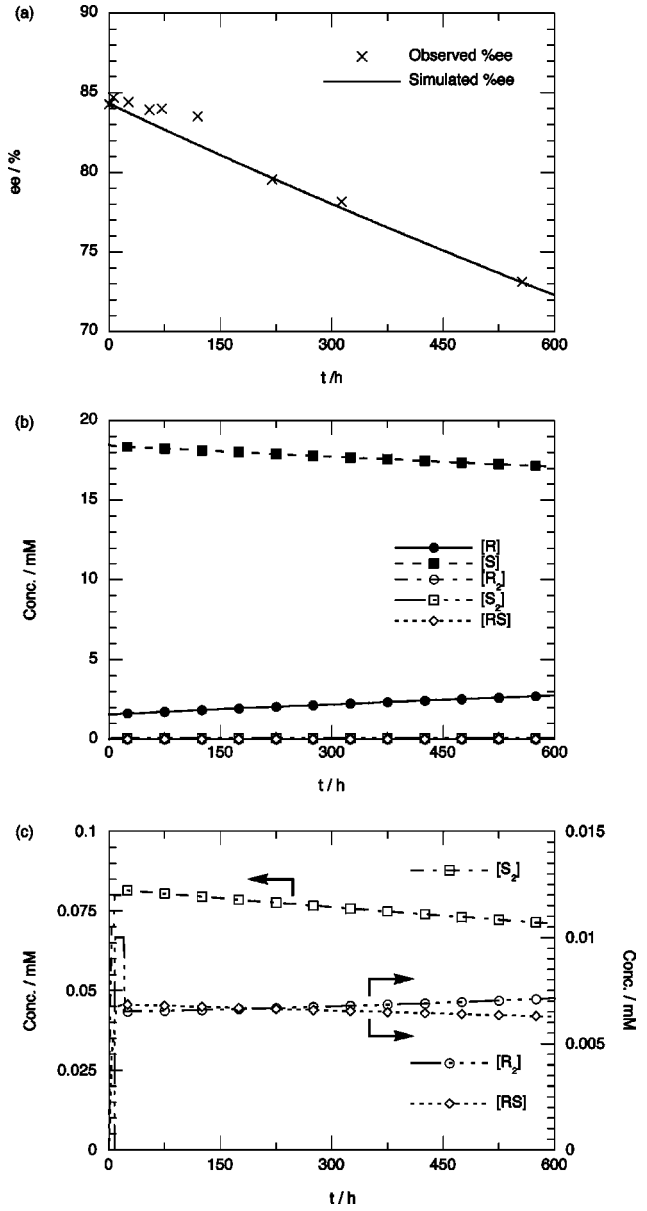


Figure 3. (a) Racemization of (*S*)-rich **2** (84% ee) in $CHCl_3$ (20.0 mM) at 20 °C and the time course of the simulated ee value that was evaluated by the equation ([**S**] + 2[$\mathbf{S_2}$] − [**R**] − 2[$\mathbf{R_2}$])/([**S**] + 2[$\mathbf{S_2}$] + [**R**] + 2[$\mathbf{R_2}$] + 2[**RS**]) × 100. (b) Changes in the concentrations of the five species with the elapse of time. (c) Enlargement of changes in the concentrations of $\mathbf{R_2}$, $\mathbf{S_2}$, and **RS** in panel b.

generated one million sets of the six rate constants at random and then simulated the time-courses of the concentrations of the five species for each set. The sum of residuals between the observed and calculated concentrations of **R** and **S** was employed to deduce the best rate constants. As can be seen from Figure 3a, racemization of (*S*)-enriched **2** was satisfactorily reproduced by the simulation using the best rate constants shown in Scheme 2.

From the kinetic constants summarized in Scheme 2, the observed spontaneous racemization of (*S*)-rich **2** can be accounted for as follows. As shown in Figure 3c, in a solution of (*S*)-rich **2** the homochiral dimerization of the monomers 2**S** occurs. The resultant $\mathbf{S_2}$ is slowly converted to the heterodimer **RS** because the rate constant (k_{23}) is smaller than that of the competitive dissociation pathway to the initial 2**S** (k_{21}). Nonetheless, once the heterodimer **RS** is formed, the conversion from **RS** into either homodimer $\mathbf{R_2}$ or $\mathbf{S_2}$ occurs smoothly with identical probabilities because the dissociation of **RS** to its component monomers **R** and **S** is strongly hampered by the smaller rate constant k_{43} as compared with the conversion to $\mathbf{R_2}$ or $\mathbf{S_2}$ (k_{32}). As a final step, $\mathbf{R_2}$ rapidly dissociates to its component monomers 2**R** due to the large k_{21}. The initial formation of $\mathbf{S_2}$ from 2**S** as well as the subsequent conversion of $\mathbf{S_2}$ to **RS** are kinetically unfavorable, whereas the involvement of these processes is assumed to eventually decrease the ee value of **2** with the aid of the kinetically favorable conversion of **RS** to $\mathbf{R_2}$ and its dissociation to 2**R**. As a consequence, it was found from kinetic considerations that the intermolecular association, which triggered the subsequent multistep racemization processes shown in Scheme 1, had a key role to play in the observed spontaneous racemization of **2**.

In summary, we have found that enantiomerically enriched *trans*-**1**, **2**, and *trans*-**3** exhibit spontaneous racemization and/or epimerization behavior in solution, which can be interpreted in terms of multistep equilibrations initiated by intermolecular abstraction of the phenolic hydrogen atom by the NO radical in aprotic solvents and have satisfactorily been suppressed by the use of protic solvents or hydrogen bonding acceptor solvents, which can prevent the NO radical from approaching the phenolic OH group by solvation.

Supporting Information Available: Experimental procedures and spectral data for *trans*-(2*S*,5*S*)-**1**, (2*S*)-**2**, *trans*-(2*S*,5*S*)-**3**, (2*S*)-**4**, and (2*S*)-**5** and chromatograms of HPLC analysis for *trans*-(2*S*,5*S*)-**1**, (2*S*)-**2**, and *trans*-(2*S*,5*S*)-**3**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL050401P