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First Example of Memory of Chirality in Carbenium Ion Chemistry

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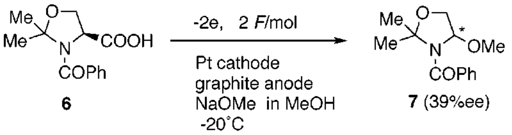
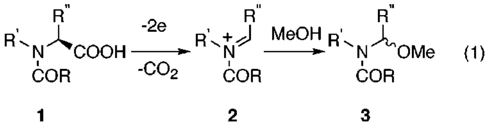
ABSTRACT



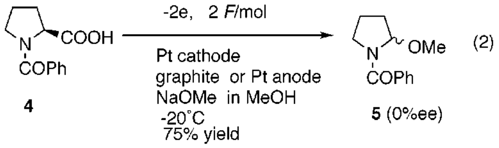
The non-Kolbe reaction of *N*-benzoyloxazolidine derivatives 6 derived from L-serine gave optically active *N,O*-acetals 7 when graphite was used as an anode material. This reaction represents the first example of “memory of chirality” in carbenium ion chemistry. The material used for the anode was critical for the memory of chirality. The substitution of carboxyl group with methoxyl group was found to proceed with an inversion mechanism.

Memory of chirality, which does not require any additional auxiliaries, is a current topic in organic synthesis.[1] This may provide a new convenient route for the synthesis of optically active compounds. To our knowledge, however, there has been no previous report of memory of chirality in carbenium ion chemistry, while there are few examples in carbanion chemistry, where achiral enolates prepared from chiral bulky ketones or esters were trapped with electrophiles.[2] We report here the first memory of chirality in carbenium ion chemistry.

The electrochemical oxidation of *N*-acyl-α-amino acids **1** in methanol gives *N,O*-acetals **3** (a non-Kolbe reaction)[3] (eq 1).[4]



Since this oxidation proceeds through carbenium ion intermediates **2**, which are stabilized by the adjacent nitrogen atom, it should give racemic acetals **3** from optically active **1**. In fact, the electrolysis of *N*-benzoylated L-proline (**4**) gave racemic *N,O*-acetal **5** regardless of the material used as the anode (eq 2).



In contrast with the non-Kolbe reaction of **4**, that of L-serine derivative **6**[5] gave an optically active α-methoxylated product **7** in 39% ee when graphite was used as the anode material (eq 3). The absolute configuration of the enriched isomer of **7** could not be determined but it was estimated to be *S* on the basis of the results described below. Although

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(1) (a) Seebach, D.; Sting, A. R.; Hoffmann, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2708−2748. (b) Fuji, K.; Kawabata, T. *Chem. Eur. J.* **1998**, *4*, 373−376.

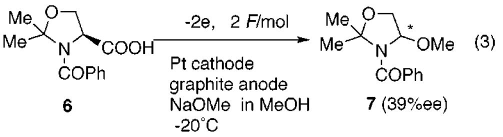
(2) (a) Seebach, D.; Wasmuth, M. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 971−972. (b) Kawabata, T.; Yashiro, K.; Fuji, K. *J. Am. Chem. Soc.* **1991**, *113*, 9694−9695. (c) Beagley, B.; Betts, M. J.; Pritchard, R. G.; Schofield, A.; Stoodley, R. J.; Vohra, S. *J. Chem. Soc., Chem. Commun.* **1991**, 924−925. (d) Gees, T.; Schweiser, W. B.; Seebach, D. *Helv. Chim. Acta*. **1993**, *76*, 2640−2653. (e) Kawabata, T.; Wirth, T.; Yashiro, K.; Suzuki, H.; Fuji, K. *J. Am. Chem. Soc.* **1994**, *116*, 10809−10810.

(3) Schäfer, H. J. *Top. Curr. Chem.* **1990**, *152*, 91−151.

(4) (a) Iwasaki, T.; Horikawa, H.; Matsumoto, K.; Miyoshi, M. *J. Org. Chem.* **1979**, *44*, 1552. (b) Shono, T.; Matsumura, Y.; Tsubata, K.; Uchida, K. *J. Org. Chem.* **1986**, *51*, 2590−2592. (c) Zietlow, A.; Steckhan, E. *J. Org. Chem.* **1994**, *59*, 5658−5661.

10.1021/ol005795t CCC: $19.00

the ee of **7** was still not satisfactory, this oxidation is the first reaction in which the original chirality was retained through carbenium ion intermediates.



6

7 (39%ee)

A typical procedure for the non-Kolbe reaction is as follows. A solution of **6** (0.5 mmol) and NaOMe (0.6 mmol) in methanol (10 mL) was charged in a one-compartment cell equipped with a graphite plate anode (1 cm × 2 cm) and a platinum plate cathode (1 cm × 2 cm). After 2*F*/mol of electricity was passed through the cell at −20 °C with a constant current (50 mA), the usual workup gave **7**, the ee of which was determined by chiral HPLC analysis. The electrolysis of **6** was also carried out under several other reaction conditions. The results are summarized in Table 1, which shows an interesting effect of the anode material on the yield and ee of **7**. Among the anode materials examined, only graphite[6] gave a positive result concerning the ee of **7** (entries 1−3), while other materials, such as glassy carbon, Pt, and Au, gave racemic **7** (entries 4−6). The kind of base did not affect the ee (entries 1−3).

Table 1. The non-Kolbe reaction of **6**[a,b]

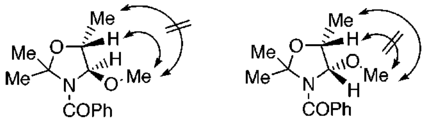
entry	anode	base (equiv.) [c]	Isolated yield (%) of **7**	ee (%) [d] of **7**
1	graphite	NaOMe (1.2)	69	39
2	graphite	Et_3N (0.3)	79	35
3	graphite	Pyridine (1.2)	77	37
4	glassy carbon	NaOMe (1.2)	51	0
5	Pt	NaOMe (1.2)	~100	0
6	Au	NaOMe (1.2)	45	0

[a] Electrolysis of **6** (0.5mmol) in MeOH (10mL) was carried out at -20°C. [b] Pt plate (1cm x 2cm) cathode was used. [c] Equiv. to **6**. [d] Determined by HPLC analysis employing a Daicel Chiralpak AD.

To clarify the cause of the memory of chirality observed in entries 1−3, we carried out various experiments. First, optically active **7** might be formed by a **6**-catalyzed enantioselective exchange of a methoxyl group of racemic **7** with methanol. This possibility was dismissed based on the finding that no optically active **7** was formed by mixing a solution of racemic **7** and **6** in methanol or in methanol containing 5% formic acid at −20 °C.

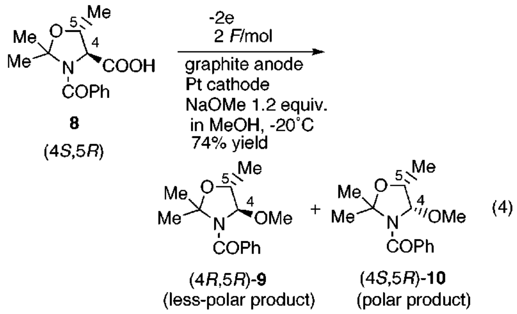
Next, it is possible that optically active **7** was formed by electrolysis using a platinum anode but this optically active **7** was immediately racemized by electrochemically generated acids.[7] However, electrolysis of optically active **7** (39% ee) in methanol using a platinum anode resulted in the recovery of optically active **7** (39% ee), indicating that the electrolysis of **6** using a platinum anode produced racemic **7** but no optically active **7**. Third, to compare electrochemical oxidation in a heterogeneous system with oxidation in a homogeneous system, the chemical oxidation of **6** by lead tetraacetate was attempted (1 equiv of lead tetraacetate in methanol at −20 °C for 3 h). As a result, racemic **7** (0% ee) was formed in 7% yield.[8] These results suggest that a graphite anode might play an important role in the generation of optically active **7**.

A similar memory of chirality was observed in the non-Kolbe reactions of L-threonine and L-*allo*-threonine derivatives (**8** and **11**, respectively) (eqs 4 and 5), which were carried out under conditions similar to those used for the transformation of **6** to **7**. The electrolyses gave decarboxylated products consisting of stereoisomers (a mixture of the less-polar product **9** and the polar product **10**) which were separable by means of column chromatography.[9] The NOESY data of **9** and **10** suggest that **9** and **10** have a trans and cis relationship between 4-methoxyl and 5-methyl groups, respectively. Figure 1 shows the NOESY data of **9** and **10** from **8**. Thus, we estimated that the products from **8** (4*S*,5*R*-isomer) were (4*R*,5*R*)-**9** and (4*S*,5*R*)-**10**, and the products from **11** (4*S*,5*S*-isomer) were (4*S*,5*S*)-**9** and (4*R*,5*S*)-**10**. The ratios of the stereoisomers in these reactions are noteworthy. The electrolysis of **8** gave a ratio of 35 to 65, in contrast to the ratio of 80 to 20 observed in the electrolysis of **11**.



(4*R*,5*R*)-**9** (less-polar) (4*S*,5*R*)-**10** (polar)

Figure 1. NOESY data for **9** and **10** obtained from **8**. Arrows indicate NOE. Arrows with // indicate no NOE.



8
(4*S*,5*R*)

(4*R*,5*R*)-**9** (less-polar product)

(4*S*,5*R*)-**10** (polar product)

(4*R*,5*R*)-**9** : (4*S*,5*R*)-**10** = 35 : 65

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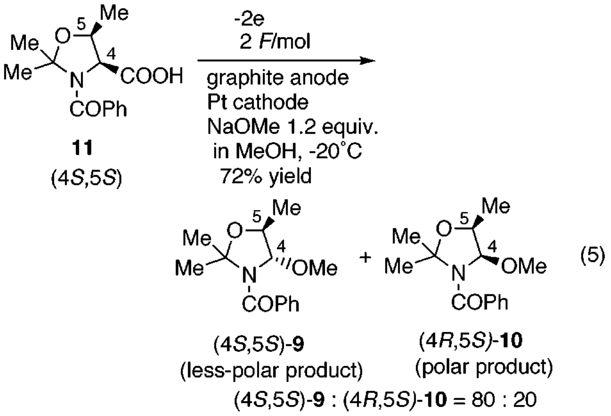
(5) Compound **6** was prepared from L-serine, see; Garner, P.; Park, J. M. *J. Org. Chem.* **1987**, *52*, 2361−2364.

(6) G347 graphite plate (Tokai Carbon Co., Ltd.) was used as an anode.

(7) Electro-generated acids can be formed in the vicinity of an anode; Baizer, M. M. In *Organic Electrochemistry*; Lund, H., Baizer, M. M., Eds.; Marcel Dekker: New York, 1991; Chapter 30.

(8) The starting material **6** was mainly recovered.



On the other hand, the non-Kolbe reaction of **8** and **11** using a platinum anode resulted in the formation of a mixture of (4*R*,5*R*)-**9** and (4*S*,5*R*)-**10** (eq 6) and a mixture of (4*S*,5*S*)-**9** and (4*R*,5*S*)-**10** (eq 7) with respective ratios of 55 to 45, which is a thermodynamic ratio.[10]

$$\mathbf{8} \xrightarrow[\substack{\text{Pt anode} \\ \text{Pt cathode} \\ \text{NaOMe 1.2 equiv.} \\ \text{in MeOH, -20°C} \\ \text{72\% yield}}]{\substack{\text{-2e} \\ 2\ F\text{/mol}}} \underset{55\ :\ 45}{(4R,5R)\text{-}\mathbf{9} \; + \; (4S,5R)\text{-}\mathbf{10}} \quad (6)$$

$$\mathbf{11} \xrightarrow[\substack{\text{Pt anode} \\ \text{Pt cathode} \\ \text{NaOMe 1.2 equiv.} \\ \text{in MeOH, -20°C} \\ \text{70\% yield}}]{\substack{\text{-2e} \\ 2\ F\text{/mol}}} \underset{55\ :\ 45}{(4S,5S)\text{-}\mathbf{9} \; + \; (4R,5S)\text{-}\mathbf{10}} \quad (7)$$

These results show that the oxidative replacement of the carboxyl group of **8** and **11** with the methoxyl group mainly proceeded with an inversion when graphite was used as an anode, while the use of a platinum anode instead of a graphite anode gave a mixture of the stereoisomers (**9** and **10**) with a thermodynamically stable ratio. On the basis of these results, we can estimate the absolute configuration at the 4-position of an enriched isomer of **7** to be *S* and thus, an enriched isomer of **7** as an inversion product.

In summary, we have presented the first memory of chirality in carbenium ion chemistry. Although it is not clear why the non-Kolbe reaction of **6**, **8**, and **11** gave optically active decarboxylated products when a graphite anode was used, an interaction between the carbenium ion intermediates and the graphite anode seems to be important for the generation of the optically active products. On the other hand, there may be little adsorption of carbenium ion intermediates on a platinum anode.[11]

Further studies on mechanistic aspects, improvement of the ee, and the stereochemistry are currently underway.

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Supporting Information Available: The characterization data and/or HPLC traces for **6**−**11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[9] Silica gel, AcOEt/hexane = 1/5.

[10] Treatment of (4*R*,5*R*)-**9** with 5% formic acid in methanol (at −20 °C for 90 h) gave a mixture of (4*R*,5*R*)-**9** and (4*S*,5*R*)-**10** in a ratio of 55/45.

[11] The difference between graphite and Pt in the electrochemical oxidation of organic compounds has been reported previously. Ross, S. D.; Finkelstein, M. *J. Org. Chem.* **1969**, *34*, 2923−2927.