Influence of the Conformation of Methoxy-(2-naphthyl)acetates (2NMA Esters) on Their Chemical Reactions

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An S_N2 reaction (NaI) of 1,7-di(methanesulfoxy)heptadien-4-yl methoxy-(2-naphthyl)acetate and a tributyltin hydride reduction of 1,7-diiodo-4-yl methoxy-(2-naphthyl)acetate (2NMA) is crucial for determination of the absolute configuration of secondary alcohols.

Key words 2NMA; chiral anisotropic reagent; conformation; steric effect

Methoxy-(2-naphthyl)acetic acid (2NMA)^{1–2)} is a potent chiral anisotropic reagent used for the determination of the absolute configuration of secondary alcohols. The methodology is based on the stable conformation of the 2NMA ester (Fig. 1[A]), in which the carbonyl proton, methoxy, and carbonyl oxygen are oriented in the same plane, causing the upfield proton chemical shifts of the R group, which is on the same side as the naphthyl group, in the ¹H-NMR spectrum. This conformation of the 2NMA esters has been confirmed by X-ray crystallography²⁾ and molecular dynamics calculations.³⁾

It would be interesting to know if this stable conformation of the 2NMA moiety can influence chemical reactions carried out on the type [B compounds], in which two substituents (R) of the carbinol part are identical. This paper reports that the conformation of the 2NMA moiety does actually affect the course of organic reactions.

At first, an S_N2 reaction of dimesylate (**1**) with sodium iodide was examined. The dimesylate was prepared by the following procedure: Commercially available 1,6-heptadien-4-ol was condensed with racemic 2NMA (EDC, DMAP, CH₂Cl₂), followed by hydroboration ((CH₃)₂S·BH₃, THF) to give the diol, which afforded dimesylate (**1**) by treatment with mesyl chloride in pyridine.

A solution of the dimesylate (**1**; 9.5 μmol) and sodium iodide (2.4 eq) in deuterioacetone (0.5 ml) was placed in a 5 mm-NMR tube, and the reaction course was monitored by recording the ¹H-NMR spectra at 32 °C. The *syn*- (to the 2-naphthyl group) and *anti*-side mesyloxymethylene (CH₂OMs) signals of **1** were easily distinguished by their chemical shifts:^{1–2)} the *syn*-side CH₂ signal appeared further upfield (δ 3.84) than that of the *anti*-side CH₂ (δ 4.27) due to the strong anisotropic effect of the naphthalene ring.

The reaction course is shown in Fig. 2a. The signal intensities of the *syn*-side (closed square) and *anti*-side (closed triangle) methylene protons are plotted against reaction time. As can be seen in the graph, there is a significant difference in the reaction rate between the *syn*-CH₂ and *anti*-CH₂. The signal of the latter decreases more rapidly than that of the former ($k_{anti}/k_{syn}=1.83$).

The same tendency was observed (Fig. 2b) in a radical reaction performed on diiodide (**4**). The iodide was obtained by treating **1** with sodium iodide in acetone. As in the case of dimesylate (**1**), the proton NMR (C₆D₆) signals of *syn*-CH₂I and *anti*-CH₂I of **4** appeared upfield (δ 2.42) and downfield (δ 2.60), respectively. A solution of **4**, tributyltin hydride (TBTH) (2.4 eq), and a small amount of α,α'-azobisisobutyronitrile (AIBN) in C₆D₆ was sealed in an NMR tube under an argon atmosphere, and the tube was placed in a water bath (30 °C). The ¹H-NMR spectra were recorded at 60 minute intervals, and the results are shown in Fig. 2b. The intensity of the *syn*-CH₂I decreases more quickly than that of the *anti*-CH₂I ($k_{anti}/k_{syn}=1.13$).

These phenomena can be explained by the stable conformation of the 2NMA ester (Fig. 3[A]). The naphthyl group prevents the approach of the reagents (NaI and TBTH) from the *syn*-side. When the iodide anion attacks the *syn*-CH₂OMs from the remoter side of the 2NMA moiety, the leaving me-

Fig. 1. [A] The Stable Conformation of an (*R*)-2NMA Ester of a Secondary Alcohol and [B] A Newman Model of an (*R*)-2NMA Ester of the Secondary Alcohol, in Which Two Alkyl Substituents (R) Are Identical

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syloxy group may also be hindered by the naphthyl group, thus resulting in the larger k_{anti}/k_{syn} value than that of the tin hydride reduction.

We next examined the epoxidation reaction of a diallyl compound (**8**) by treatment with 2 eq of *m*-chloroperbenzoic acid (MCPBA) in $CDCl_3$. In this experiment, the intensity of the vinyl proton ($=CH-CH_2-$: δ_{syn-H} 5.44, δ_{anti-H} 5.70) sig-

nals of **8** was monitored. The results are shown in Fig. 2c. Surprisingly, the intensity of the *syn*-proton decreased faster than that of the *anti*-proton ($k_{anti}/k_{syn}=0.84$) unlike the S_N2 reaction and the butyltin hydride reduction. When the reaction was worked up after 20 h, *syn*-epoxide (**9**), *anti*-epoxide (**10**), and diepoxide were isolated in a 6:4:5 ratio.

Although the preferential epoxidation of the *syn*-vinyl group is difficult to explain one possible explanation of this finding is the participation of the naphthyl group in stabilizing the positive charge of the transition state (Fig. 3[B]). Further experiments to identify such preferential *syn*-epoxidation are in progress.

Experimental

General Experimental Procedures 1H -NMR spectra were recorded on a Bruker ARX-400 NMR spectrometer. Chemical shifts are reported in parts per million (ppm) relative to $CHCl_3$ (δ 7.25), and coupling constants are given in Hz. Mass spectra were recorded on JEOL JMS-SX102A and JEOL JMS-AM150 mass spectrometers.

1,7-Di(methanesulfonyl)heptadien-4-yl Methoxy-(2-naphthyl)acetate (1) 1,6-Heptadien-4-ol (694 mg, 5.4 mmol) was added to a solution of racemic methoxy-(2-naphthyl)acetic acid (2NMA) (1.3 g, 6.1 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (1.5 g, 7.8 mmol), triethylamine (1.1 ml, 7.8 mmol), and 4-(dimethylamino)pyridine (1.5 g, 11.9 mmol) in dry dichloromethane (100 ml). After the reaction mixture was stirred for 20 h at room temperature under nitrogen, it was treated with water, and the product was extracted with ethyl acetate. The ethyl acetate layer was washed with 10% citric acid and brine, then dried (sodium sulfate). Filtration and removal of the ethyl acetate *in vacuo* gave a residue which was purified by flash column chromatography (20% ethyl acetate in hexane) to give 1,6-heptadien-4-yl methoxy-(2-naphthyl) acetate (**8**) (1.5 g, 4.8 mmol, 89%). 1H -NMR ($CDCl_3$) δ : 7.89 (1H, s, ArH), 7.53 (3H, m, ArH), 7.47 (1H, dd, $J=8.5, 1.7$ Hz, ArH), 7.50 (2H, m, ArH), 5.70 (1H, ddt, $J=17.2, 10.2, 7.1$ Hz, *anti*- $CH=CH_2$), 5.44 (1H, ddt, $J=17.2, 10.2, 7.1$ Hz, *syn*- $CH=CH_2$), 5.03 (3H, m, *anti*- $CH=CH_2$ and $CH-O-2NMA$), 4.88 (1H, s, naph- CH), 4.76 (2H, m, *syn*- $CH=CH_2$), 3.44 (3H, s, $O-CH_3$), 2.32 (2H, m, *anti*- $CH_2-CH=CH_2$), 2.18 (2H, m, *syn*- $CH_2-CH=CH_2$); EI-MS m/z : 310.1590 (Calcd for $C_{20}H_{22}O_3$: 310.1569).

Dimethyl sulfide borane (392 μ l, 3.92 mmol) was added to a solution of **8** (506 mg, 1.63 mmol) in dry THF (1 ml) at 0 $^{\circ}C$. The mixture was stirred for 30 min at room temperature, and the reaction was stopped by adding water. The resulting mixture was treated with a mixed solution of 3N NaOH (1.3 ml) and 35% H_2O_2 (1 ml). After stirring for 30 min at room temperature, the product was extracted with ethyl acetate. The ethyl acetate layer was washed with brine and dried (sodium sulfate). Filtration and removal of the ethyl acetate *in vacuo* gave a residue which was purified by flash column chromatography (40% acetone in hexane) to give 1,7-dihydroxyheptan-4-yl methoxy-(2-naphthyl) acetate (301 mg, 870 μ mol, 53%): 1H -NMR ($CDCl_3$) δ : 7.91 (1H, s, ArH), 7.83 (3H, m, ArH), 7.53 (1H, dd, $J=10.1, 1.7$ Hz, ArH), 7.48 (2H, m, ArH), 4.97 (1H, m, $CH-O-2NMA$), 4.90 (1H, s, $MeO-CH$), 3.58 (2H, t, $J=6.4$ Hz, *anti*- CH_2-OH), 3.44 (3H, s, $O-CH_3$), 3.28 (2H, dt, $J=2.8, 6.4$ Hz, *syn*- CH_2-OH), 1.63 (4H, m, *anti*- $CH_2-CH_2-CH_2-OH$), 1.15 (4H, m, *syn*- $CH_2-CH_2-CH_2-OH$). EI-MS m/z : 346.1803 (Calcd for $C_{20}H_{26}O_5$: 346.1780).

Fig. 2. Time Courses of (a) Sodium Iodide and Dimesylate (**1**), (b) Tributyltin Hydride and Diiodide (**4**), and (c) MCPBA and Diallyl Compound (**8**)

Each experiment was done in duplicate, and mean values of the signal intensities were plotted against reaction time.

Fig. 3. [A] The S_N2 Reaction of Dimesylate (**1**) with Sodium Iodide, and the Tributyltin Hydride Reduction of Diiodide (**4**)

The stable conformation of the 2NMA ester is drawn. Attack on the *syn*- CH_2-OMe is prevented by the naphthyl group (a). The attack from the remoter side of the 2NMA group is also deterred because the leaving OMe group is sterically hindered by the naphthyl group.

[B] A Cation-Stabilizing Model to Interpret the Predominant Epoxidation of *syn*-Vinyl Group of **10**

Methanesulfonyl chloride (119 μ l, 1.54 mmol) was added to a solution of 1, 7-dihydroxyheptan-4-yl (2-naphthyl) methoxyacetate (222 mg, 642 μ mol) in pyridine (2 ml). The mixture was stirred for 10 min at room temperature. Water was added and the product was extracted with ethyl acetate. The ethyl acetate phase was washed with copper sulfate solution and brine, then dried (sodium sulfate). Filtration and removal of the ethyl acetate *in vacuo* gave **1** (276 mg, 550 μ mol, 86%): $^1\text{H-NMR}$ (CDCl_3) δ : 7.91 (1H, s, ArH), 7.84 (3H, m, ArH), 7.52 (1H, dd, $J=10.3$, 1.8 Hz, ArH), 7.49 (2H, m, ArH), 4.95 (1H, m, CH-O-2NMA), 4.91 (1H, s, OMe-CH), 4.17 (2H, t, $J=6.1$ Hz, *anti-CH₂-OMs*), 3.84 (2H, t, $J=6.2$ Hz, *syn-CH₂-OMs*), 3.44 (3H, s, O-CH_3), 2.95 (3H, s, *anti-mesyl*), 2.76 (3H, s, *syn-mesyl*), 1.67 (4H, m, *anti-CH₂-CH₂-CH₂-OMs*), 1.29 (4H, m, *syn-CH₂-CH₂-CH₂-OMs*). EI-MS m/z : 502.1316 (Calcd for $\text{C}_{22}\text{H}_{30}\text{O}_9\text{S}_2$: 520.1331).

S_N2* Reaction of **1* 1,7-Di(methanesulfonyl)-4-hexanol 2NMA ester (**1**) (14.4 mg, 28.6 μ mol) and NaI (10.3 mg, 68.6 μ mol) were dissolved in acetone- d_6 (1.5 ml), and aliquots (0.5 ml) were put into two 5 mm NMR tubes. The tubes were stoppered tightly with plastic caps, and then placed in a water bath (32 $^\circ\text{C}$). The NMR spectra of the samples were recorded at 180 min intervals for 780 min (Fig. 2a). One of the samples was poured into water, and the product was taken up in ethyl acetate. The evaporated residue was separated by HPLC (hexane : AcOEt = 7 : 3), giving mono- (**2** and **3**) and diiodides (**4**) (**2** : **3** : **4** = 4 : 2 : 5). (*R**)-1-iodo-7-mesyloxyheptan-4-yl (*S**)-methoxy-(2-naphthyl)acetate (**2**): $^1\text{H-NMR}$ (CDCl_3) δ : 7.97 (1H, s, ArH), 7.84 (3H, m, ArH), 7.53 (1H, dd, $J=10.3$, 1.8 Hz, ArH), 7.50 (2H, m, ArH), 4.96 (1H, m, CH-O-2NMA), 4.91 (1H, s, OMe-CH), 3.84 (2H, t, $J=6.4$ Hz, $\text{CH}_2\text{-OMs}$), 3.44 (3H, s, O-CH_3), 3.12 (2H, t, $J=8.0$ Hz, $\text{CH}_2\text{-I}$), 2.76 (3H, s, *mesyl*), 1.72 (4H, m, $\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-I}$), 1.41 (4H, m, $\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-OMs}$). EI-MS m/z : 534.0608 (Calcd for $\text{C}_{21}\text{H}_{27}\text{O}_6\text{SI}$: 534.0532). (*S**)-1-Hydroxy-7-iodoheptan-4-yl (*S**)-methoxy-(2-naphthyl)acetate (**3**): $^1\text{H-NMR}$ (CDCl_3) δ : 7.90 (1H, s, ArH), 7.85 (3H, m, ArH), 7.51 (3H, m, ArH), 4.96 (1H, m, CH-O-2NMA), 4.91 (1H, s, OMe-CH), 4.17 (2H, t, $J=6.4$ Hz, $\text{CH}_2\text{-OMs}$), 3.44 (3H, s, O-CH_3), 2.95 (3H, s, *mesyl*), 3.12 (2H, t, $J=7.2$ Hz, $\text{CH}_2\text{-I}$), 1.69 (4H, m, $\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-I}$), 1.41 (4H, m, $\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-OMs}$). EI-MS m/z : 534.0538 (Calcd for $\text{C}_{21}\text{H}_{27}\text{O}_6\text{SI}$: 534.0532). 1,7-Diiodoheptan-4-yl methoxy-(2-naphthyl)acetate (**4**): $^1\text{H-NMR}$ δ : 7.97 (1H, s, ArH), 7.67 (4H, m, ArH), 7.28 (2H, m, ArH), 4.82 (1H, s, MeO-CH), 4.78 (1H, m, CH-O-2NMA), 3.27 (3H, s, O-CH_3), 2.60 (2H, t, $J=6.8$ Hz, *anti-CH₂-I*), 2.42 (2H, t, $J=6.6$ Hz, *syn-CH₂-I*), 1.12—1.50 (8 H, m, $\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-I}$). EI-MS m/z : 565.9772 (Calcd for $\text{C}_{20}\text{H}_{24}\text{O}_3\text{I}_2$: 565.9733).

Tin Hydride Reduction of **4** 1,7-Diiodo-4-hexanol 2NMA ester (**4**) (21 mg, 37 μ mol), AIBN (α,α' -azobisisobutyronitrile) (1 mg, 6 μ mol), and tributyltin hydride (26 mg, 89 μ mol) were dissolved in C_6D_6 (3 ml), and aliquots (0.5 ml) of the solution were put into three 5 mm NMR tubes. The tubes were sealed under argon, and placed in a water bath (32 $^\circ\text{C}$). The ^1H -

NMR spectra of the samples were recorded at 60 min intervals for 650 min. One of the sample was evaporated and separated into **5**—**7** (**5** : **6** : **7** = 1 : 1 : 4) by HPLC (hexane : AcOEt = 95 : 5).

5: $^1\text{H-NMR}$ δ : 7.91 (1H, s, ArH), 7.84 (3H, m, ArH), 7.54 (1H, dd, $J=8.8$, 1.2 Hz, ArH), 7.48 (2H, m, ArH), 4.94 (1H, m, CH-O-2NMA), 4.89 (1H, s, MeO-CH), 3.44 (3H, s, O-CH_3), 2.78 (2H, t, $J=7.6$, $\text{CH}_2\text{-I}$), 1.20—1.65 (8 H, m, $\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-I}$, $\text{CH}_2\text{-CH}_2\text{-CH}_3$), 0.88 (3H, t, $J=7.2$, $\text{CH}_2\text{-CH}_2\text{-CH}_3$). EI-MS m/z : 440.0842 (Calcd for $\text{C}_{20}\text{H}_{25}\text{O}_3\text{I}$: 440.0808).

6: $^1\text{H-NMR}$ δ : 7.91 (1H, s, ArH), 7.84 (3H, m, ArH), 7.54 (1H, dd, $J=8.8$, 1.2 Hz, ArH), 7.48 (2H, m, ArH), 4.94 (1H, m, CH-O-2NMA), 4.84 (1H, s, MeO-CH), 3.45 (3H, s, O-CH_3), 3.09 (2H, t, $J=7.6$ Hz, $\text{CH}_2\text{-I}$), 0.80—1.80 (8H, m, $\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-I}$, $\text{CH}_2\text{-CH}_2\text{-CH}_3$), 0.64 (3H, t, $J=7.2$ Hz, $\text{CH}_2\text{-CH}_3$). EI-MS m/z : 440.0878 (Calcd for $\text{C}_{20}\text{H}_{25}\text{O}_3\text{I}$: 440.0808).

7: $^1\text{H-NMR}$ δ : 7.91 (1H, s, ArH), 7.84 (3H, m, ArH), 7.54 (1H, dd, $J=8.8$, 1.2 Hz, ArH), 7.48 (2H, m, ArH), 4.94 (1H, m, CH-O-2NMA), 4.84 (1H, s, MeO-CH), 3.45 (3H, s, O-CH_3), 0.89—1.64 (8H, m, $\text{CH}_2\text{-CH}_2\text{-CH}_3$), 0.85 (3H, t, $J=7.6$ Hz, *anti-CH₂-CH₂-CH₃*), 0.63 (3H, t, $J=7.2$ Hz, *syn-CH₂-CH₂-CH₃*). EI-MS m/z : 314.1876 (Calcd for $\text{C}_{20}\text{H}_{26}\text{O}_3$: 314.1882).

Epoxidation Reaction 1,6-Heptadien-4-ol 2NMA ester (**8**) (10 mg, 32 μ mol) and *m*-chloroperbenzoic acid (12 mg, 69 μ mol) were dissolved in CDCl_3 (1.5 ml), and aliquots (0.5 ml) of the solution were placed into two 5 mm NMR tubes. These tubes were put in a water bath and the $^1\text{H-NMR}$ spectra were recorded at 60 min intervals for 46 h. The samples were diluted with ethyl acetate and washed with saturated sodium thiosulfate and sodium hydrogencarbonate solution. After concentration and purification by preparative TLC, *anti*-epoxide **9** (3.7 mg) and *syn*-epoxide **10** (6.1 mg) were obtained as a mixture of diastereomers, respectively. **9**: $^1\text{H-NMR}$ (CDCl_3) δ : 7.90 (1H, s, ArH), 7.83 (3H, m, ArH), 7.52 (3H, m, ArH), 5.46 (1H, m, CH=CH_2), 5.15 (1H, m, CH-O-2NMA), 4.91—4.93 (1H, s, MeO-CH), 4.77 (2H, m, CH=CH_2), 3.46 (3H, s, O-CH_3), 2.23 (2H, m, $\text{CH}_2\text{-CH=CH}_2$), 1.78—2.93 (5H, m, $\text{CH}_2\text{-epoxide}$); EI-MS m/z : 326.1524 (Calcd for $\text{C}_{20}\text{H}_{22}\text{O}_4$: 326.1518).

10: $^1\text{H-NMR}$ (CDCl_3) δ : 7.90 (1H, s, ArH), 7.83 (3H, m, ArH), 7.52 (3H, m, ArH), 5.70 (1H, m, CH=CH_2), 5.18 (1H, m, CH-O-2NMA), 5.07 (2H, m, CH=CH_2), 4.88—4.91 (1H, s, MeO-CH), 3.44—3.35 (3H, s, O-CH_3), 2.40 (2H, m, $\text{CH}_2\text{-CH=CH}_2$), 1.60—2.57 (5H, m, $\text{CH}_2\text{-epoxide}$).

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