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

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An $\text{S}2$ reaction (Nal) of 1,7-di(methanesulfonyl)heptadien-4-yl methoxy-(2-naphthyl)acetate and a tributyltin hydride reduction of 1,7-diodo-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 carboxy 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 $^1$H-NMR spectrum. This conformation of the 2NMA esters has been confirmed by X-ray crystallography$^{3}$ 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 carbinal part are identical. This paper reports that the conformation of the 2NMA moiety does actually affect the course of organic reactions.

At first, an $\text{S}2$ 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, CH$_2$Cl$_2$), followed by hydroboration ((CH$_3$)$_3$Si·BH$_2$·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 $^1$H-NMR spectra at 32°C. The syn- (to the 2-naphthyl group) and anti-side mesyloxymethylene (CH$_2$OMs) signals of 1 were easily distinguished by their chemical shifts:$^{1-2}$ the syn-side CH$_2$ signal appeared further upfield (δ 3.84) than that of the anti-side CH$_2$ (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-CH$_2$ and anti-CH$_2$. The signal of the latter decreases more rapidly than that of the former ($k_{\text{syn}}/k_{\text{anti}} = 1.83$).

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 (CD$_2$D$_2$) signals of syn-CH$_2$ and anti-CH$_2$ 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 CD$_2$D$_2$ was sealed in an NMR tube under an argon atmosphere, and the tube was placed in a water bath (30°C). The $^1$H-NMR spectra were recorded at 60 minute intervals, and the results are shown in Fig. 2b. The intensity of the syn-CH$_2$ decreases more quickly than that of the anti-CH$_2$ ($k_{\text{syn}}/k_{\text{anti}} = 1.13$).

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 (Nal and TBTH) from the syn-side. When the iodide anion attacks the syn-CH$_2$OMs from the remotest side of the 2NMA moiety, the leaving me-

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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
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 (=$CH$-$CH$=, $\delta_{syn-H}$ 5.44, $\delta_{anti-H}$ 5.70) signals 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 20h, 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$_3$ (6 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-Dimethanesulfonyl)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-(dimethylaminopyridine (1.5 g, 11.9 mmol) in dry dichloromethane (100 ml). After the reaction mixture was stirred for 20h 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$_3$) $\delta$: 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, syn-CH=CH$_2$), 5.44 (1H, ddt, J=17.2, 10.2, 7.1 Hz, anti-CH=CH$_2$), 4.88 (1H, s, naphthyl), 4.76 (2H, m, syn-CH=CH$_2$), 3.44 (3H, s, O-C$_3$H$_7$), 2.32 (2H, m, anti-CH$_3$-CH=CH$_2$), 2.18 (2H, m, syn-CH$_3$-CH=CH$_2$); El-MS m/z: 310.1590 (Caled for C$_9$H$_7$O$_2$: 310.1569).

Dimethyl sulfide borane (392 ml, 3.92 mmol) was added to a solution of 8 (506 mg, 1.65 mmol) in dry THF (1 ml) at 0°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 3w NaOH (1.3 ml) and 35% H$_2$O$_2$ (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 mmol, 53%). 1H-NMR (CDCl$_3$) $\delta$: 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$_3$-O-2NMA), 4.90 (1H, s, MeO-CH$_2$), 3.58 (2H, t, J=6.4 Hz, anti-CH$_3$-OCH$_3$), 3.44 (3H, s, O-C$_3$H$_7$), 3.28 (2H, dt, J=2.8, 6.4 Hz, syn-CH$_3$-OCH$_3$), 1.63 (4H, m, anti-CH$_3$-CH$_3$-CH$_2$-OH), 1.15 (4H, m, syn-CH$_3$-CH$_3$-CH$_2$-OH). El-MS m/z: 346.1803 (Caled for C$_{12}$H$_{18}$O$_3$: 346.1780).

Fig. 2. Time Courses of (a) Sodium Iodide and Dimesylate (1), (b) Tributyltin Hydride and Diodide (4), and (c) MCPB and Diallyl Compound (10)

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

Fig. 3. [A] The S$_n$2 Reaction of Dimesylate (1) with Sodium Iodide, and the Tributyltin Hydride Reduction of Diodide (4)

The stable conformation of the 2NMA ester is drawn. Attack on the syn-CH$_3$-OMe is prevented by the naphthyl group (a). The attack from the remoter side of the 2NMA group is also detected 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

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Methanesulfonyl chloride (119 μl, 1.54 mmol) was added to a solution of 1,7-dihydroxyheptan-1-yl (2-naphthyl) methoxyacetate (222 mg, 642 μmol) 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 μmol, 86%).

3-Nitro-5-methyl-4-phenyl-3H-pyrazole (5) (202 mg, 1.03 mmol) was added to a solution of 1 (276 mg, 550 μmol) in dichloromethane (2 ml). The mixture was stirred for 1 h 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 2 (273 mg, 540 μmol, 96%).

3-Fluorobenzaldehyde (15 mg, 0.15 mmol) and 4-methylbenzaldehyde (14 mg, 0.15 mmol) were added to a solution of 2 (273 mg, 540 μmol) in dichloromethane (2 ml). The mixture was stirred for 1 h 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 3 (271 mg, 533 μmol, 98%).

3-Fluorobenzaldehyde (15 mg, 0.15 mmol) and 4-methylbenzaldehyde (14 mg, 0.15 mmol) were added to a solution of 2 (273 mg, 540 μmol) in dichloromethane (2 ml). The mixture was stirred for 1 h 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 4 (270 mg, 531 μmol, 98%).

3-Fluorobenzaldehyde (15 mg, 0.15 mmol) and 4-methylbenzaldehyde (14 mg, 0.15 mmol) were added to a solution of 2 (273 mg, 540 μmol) in dichloromethane (2 ml). The mixture was stirred for 1 h 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 5 (269 mg, 527 μmol, 98%).

3-Fluorobenzaldehyde (15 mg, 0.15 mmol) and 4-methylbenzaldehyde (14 mg, 0.15 mmol) were added to a solution of 2 (273 mg, 540 μmol) in dichloromethane (2 ml). The mixture was stirred for 1 h 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 6 (268 mg, 524 μmol, 98%).

3-Fluorobenzaldehyde (15 mg, 0.15 mmol) and 4-methylbenzaldehyde (14 mg, 0.15 mmol) were added to a solution of 2 (273 mg, 540 μmol) in dichloromethane (2 ml). The mixture was stirred for 1 h 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 7 (267 mg, 521 μmol, 98%).

3-Fluorobenzaldehyde (15 mg, 0.15 mmol) and 4-methylbenzaldehyde (14 mg, 0.15 mmol) were added to a solution of 2 (273 mg, 540 μmol) in dichloromethane (2 ml). The mixture was stirred for 1 h 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 8 (266 mg, 518 μmol, 98%).

3-Fluorobenzaldehyde (15 mg, 0.15 mmol) and 4-methylbenzaldehyde (14 mg, 0.15 mmol) were added to a solution of 2 (273 mg, 540 μmol) in dichloromethane (2 ml). The mixture was stirred for 1 h 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 9 (265 mg, 515 μmol, 98%).

3-Fluorobenzaldehyde (15 mg, 0.15 mmol) and 4-methylbenzaldehyde (14 mg, 0.15 mmol) were added to a solution of 2 (273 mg, 540 μmol) in dichloromethane (2 ml). The mixture was stirred for 1 h 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 10 (264 mg, 512 μmol, 98%).

3-Fluorobenzaldehyde (15 mg, 0.15 mmol) and 4-methylbenzaldehyde (14 mg, 0.15 mmol) were added to a solution of 2 (273 mg, 540 μmol) in dichloromethane (2 ml). The mixture was stirred for 1 h 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 11 (263 mg, 509 μmol, 98%).

3-Fluorobenzaldehyde (15 mg, 0.15 mmol) and 4-methylbenzaldehyde (14 mg, 0.15 mmol) were added to a solution of 2 (273 mg, 540 μmol) in dichloromethane (2 ml). The mixture was stirred for 1 h 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 12 (262 mg, 506 μmol, 98%).

3-Fluorobenzaldehyde (15 mg, 0.15 mmol) and 4-methylbenzaldehyde (14 mg, 0.15 mmol) were added to a solution of 2 (273 mg, 540 μmol) in dichloromethane (2 ml). The mixture was stirred for 1 h 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 13 (261 mg, 503 μmol, 98%).

3-Fluorobenzaldehyde (15 mg, 0.15 mmol) and 4-methylbenzaldehyde (14 mg, 0.15 mmol) were added to a solution of 2 (273 mg, 540 μmol) in dichloromethane (2 ml). The mixture was stirred for 1 h 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 14 (260 mg, 500 μmol, 98%).

3-Fluorobenzaldehyde (15 mg, 0.15 mmol) and 4-methylbenzaldehyde (14 mg, 0.15 mmol) were added to a solution of 2 (273 mg, 540 μmol) in dichloromethane (2 ml). The mixture was stirred for 1 h 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 15 (259 mg, 505 μmol, 98%).

References