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ASYMMETRIC INDUCTION IN THE FREE-RADICAL ADDITION OF THIOLACETIC ACID TO DI-*l*-MENTHYL MALEATE AND DI-*l*-MENTHYL FUMARATE

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ASYMMETRIC INDUCTION IN THE FREE-RADICAL ADDITION OF THIOLACETIC ACID TO DI-*l*-MENTHYL MALEATE AND DI-*l*-MENTHYL FUMARATE

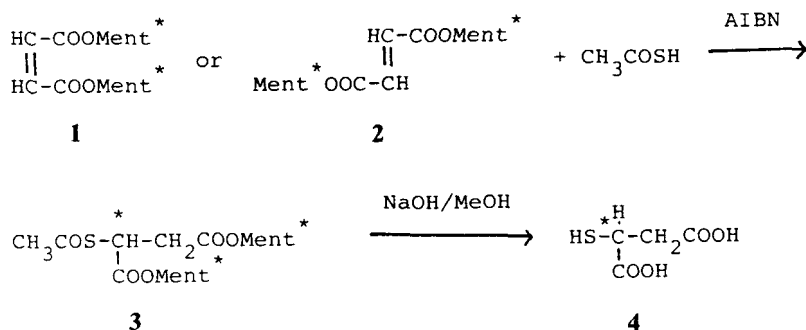
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Numerous studies of asymmetric inductions via ionic processes have been reported;¹ however, there have been few examples via free-radical processes.² Recently, we were successful in observing asymmetric induction in free-radical additions of thiolacetic acid to cyclohexanone and also to *Z*-2-octene in *l*-menthol^{3,4} and of menthyl mercaptoacetate to prochiral olefins^{5,6} (enantiofacial differentiation) and radical addition of achiral thiols to *l*-menthyl crotonate and *l*-menthyl methacrylate^{7,8} (diastereofacial differentiation).

In this paper, we wish to describe the stereochemical course of the radical addition of thiolacetic acid to di-*l*-menthyl maleate (**1**) and di-*l*-menthyl fumarate (**2**).



(**1**) was prepared by refluxing maleic anhydride (1×10^{-1} mol) and *l*-menthol (2×10^{-1} mol) in the presence of *p*-toluenesulfonic acid (1×10^{-2} mol) in benzene (100 ml) according to the usual esterification method. Yield 97%; mp 97–98°C; IR (KBr) $\nu_{\text{C=O}}$ 1710 cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3) δ = 6.15 (2 H, s), 4.76 (2 H, q) 0.70–2.25 (34 H, m); $[\alpha]_{\text{D}}^{22}$ -95.67° ($c = 1.2$, C_6H_6), (Lit.⁹ mp 98°; $[\alpha]_{\text{D}}^{18}$ -97.0°). (**2**) was prepared by refluxing (**1**) (1×10^{-1} mol) in the presence of morpholine (1×10^{-2} mol) in benzene (100 ml) for 2 hr according to Otsu's method.¹⁰ Yield 90%; mp 64–65°C; IR (KBr) $\nu_{\text{C=O}}$ 1710 cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3) δ = 6.76 (2 H, s), 4.76 (2 H, q), 0.70–2.26 (34 H, m); $[\alpha]_{\text{D}}^{22}$ -104.3° ($c = 0.90$, C_6H_6), (Lit.⁹ mp 59–60°; $[\alpha]_{\text{D}}^{18}$ -98.4°).

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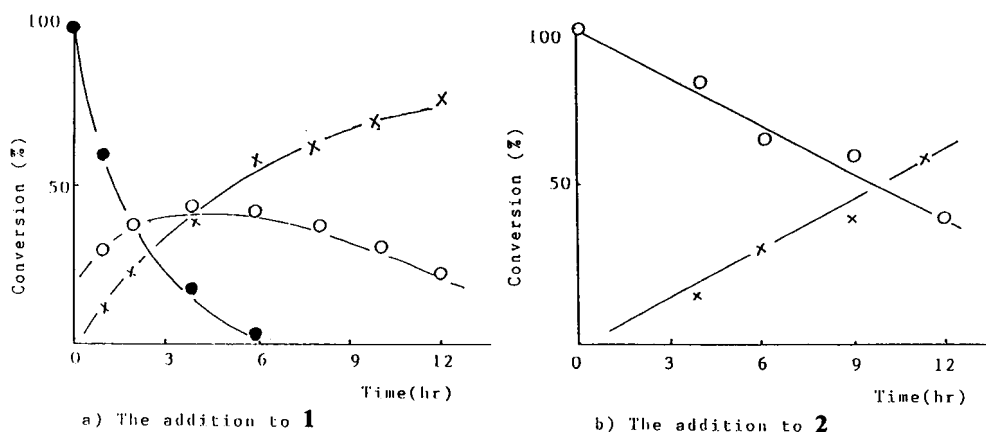


FIGURE 1 Time-conversion relations for the addition of thiol to olefin. [Thiol]/[Olefin] = 5.0. ● = **1**. ○ = **2**. × = **3**. Solvent: C₆D₆. Temp.: 80°C.

Figure 1 shows the time conversion for the addition of thiolacetic acid (6.25×10^{-5} mol) to **1** and **2** (1.25×10^{-5} mol) in the presence of a catalytic amount of 2,2'-azobisisobutyronitrile (AIBN) (1.25×10^{-6} mol) in benzene-D₆ (0.4 ml) at 80°C by ¹H-NMR spectral analysis. It may safely be said that **1** first isomerizes to **2**, perhaps through an equilibrium $\mathbf{1} \rightleftharpoons \mathbf{2}$ and the addition of thiol to **2** will take place predominantly because an initial formation of **2**, along with a rather sharp decrease of the peak of **1**, was observed in the reaction of the thiol with **1** (Figure 1a) and also no formation of **1** was detected in the reaction of the thiol with **2** (Figure 1b). This may partly be supported by the finding that essential differences in the $[\alpha]_D$ value of thiomalic acid obtained from the reaction of the thiol with either **1** or **2** was not observed (Table I). The same addition-rotation-elimination sequence was reported by Walling in the reaction of thiyl radicals with olefins.¹¹

A typical procedure for the isolation of thiomalic acid (**4**) was as follows: A mixture of **1** or **2** (1.25×10^{-4} mol) and thiolacetic acid (6.25×10^{-4} mol) in

TABLE I
Synthesis of thiomalic acid at 80°C

Substrate ^a	$\frac{[\text{Thiol}]}{[\text{Olefin}]}$ ^b	Solv. ^c	Yield (%) ^d	$[\alpha]_D^{22}$ (c, EtOH)	e.e. (%)
1	5.0	Benzene	68	+3.92°(2.30)	6.4
1	5.0	THF	72	+5.95°(2.61)	9.7
1	5.0	CCl ₄	60	+5.68°(2.06)	9.3
2	5.0	Benzene	65	+2.56°(3.80)	4.1
2	1.2	Benzene	60	+2.60°(2.20)	4.2
2	5.0	THF	63	+4.38°(3.95)	7.1
2	5.0	CCl ₄	58	+5.21°(1.94)	8.5
2	1.2	CCl ₄	62	+7.23°(2.04)	12.0

^a 1.24×10^{-4} mol.

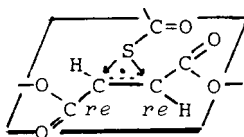
^b Thiol = 6.25×10^{-4} mol.

^c Solvent = 4 ml.

^d Isolated yield.

benzene (4 ml) containing AIBN (1.25×10^{-5} mol) was heated at 80°C for 24 hr in a degassed ampul. The solvent was evaporated *in vacuo* and the residue was purified on a silica-gel column (benzene) to give the yellow oil of the addition product (**3**) in 80% yield. $^1\text{H-NMR}$ (CDCl_3) $\delta = 4.83$ (2 H, q), 2.96 (1 H, q), 1.90 (3 H, s), 0.70–2.26 (34 H, m). The product **3** was heated in 15 ml of 25% NaOH methanol solution at 60°C for 12 hr and then the solvent was removed under reduced pressure. The residue was washed with hexane and ethyl acetate, acidified with 6N-HCl solution and extracted with ether. Evaporation of the solvent gave **4** as white crystals (68% yield), mp. $148\text{--}150^\circ\text{C}$, (lit.¹² $148\text{--}149^\circ\text{C}$).

Table I shows the optical rotation values of **4** obtained under several reaction conditions. In every case, optically active thiomalic acid was obtained. It may safely be said that alkaline hydrolysis did not lead to any racemization, since optically active **4** did not show any reduction of α value upon reheating with 25% NaOH methanol solution at 60°C for 12 hr. The absolute configuration of the acid was found to be of the *R* form.¹² Thus, it may be concluded that the thiyl radical preferentially attacks the sterically less hindered *re* face of the double bond of *l*-menthyl fumarate.



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