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Asymmetric Induction in Free Radical Additions of Thiols to Olefins

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ABSTRACT

Asymmetric inductions have been achieved in the free radical additions of (1) ℓ-menthyl mercaptoacetate to such prochiral olefins as crotonic acid, methyl crotonate, and α-methylstyrene (enantiofacedifferentiation), and (2) achiral thiols to ℓ-menthyl and isobornyl crotonates (diastereoface differentiation).

INTRODUCTION

During the course of our investigations on the radical copolymerization of styrene with polar vinyl monomers such as 2,6-dimethylpyridazine-3-one [1], methyl methacrylate [2], N,N-dimethylacrylamide [3], p-substituted-N,N-diethylcinnamamides [4], and methyl vinyl sulfoxide [5], such protic solvents as phenol and carboxylic acid were found to affect the reactivities. We postulated a hypothesis that this might be caused by the hydrogen bonding solvation to the polar group of vinyl monomer both in the ground state and in the transition state of the reaction. It was thought that a protic chiral solvent might influence the geometry of the free radical addition complex and would induce an asymmetric center in the product.

In this point of view, we found earlier that an optically active copolymer was obtained by the radical copolymerization of styrene with maleic anhydride in ℓ-menthol [6] and also that optically active addition products were obtained by the radical reaction of cyclohexanone with 2-octene in ℓ-menthol [7].

Thus, with a hope to find additional examples for asymmetric induction in a free radical addition, the reactions of a few thiols with olefins have been carried out and indeed an asymmetric induction was found to occur. Some of them were reported in previous communications [8-11].

EXPERIMENTAL

Measurements

Infrared spectra were recorded with a Jasco IRA-2 diffraction grating infrared spectrophotometer. ^{1}H NMR spectra were recorded with a Hitachi R-24 high resolution NMR spectrometer, using tetramethylsilane as an internal standard. The notations s, d, t, q, and m indicate singlet, doublet, triplet, quartet, and multiplet, respectively. MS spectra were recorded with a Shimadzu GC-MS spectrometer KLB-9000, and optical rotations were measured with a Jasco DIP-140 digital polarimeter. ORD spectra were obtained on a Jasco J-20 automatic recording spectro polarimeter. At least duplicate experiments for each reaction were done and the optical rotations reached constant values after repurification of the products.

Materials

ℓ-Menthyl mercaptoacetate (1) was prepared by refluxing an equimolar mixture of mercaptoacetic acid (2) and ℓ-menthol in the presence of p-toluenesulfonic acid in benzene. Yield: 76-85%. bp 127-128°C (3 mmHg). $[\alpha]_D^{25}$ -76.4° (c = 1, $CHCl_3$). IR (neat, cm^{-1}): 2580 (SH), 1725 (C=O), and 795 (C–S). NMR ($CDCl_3$): δ = 0.75-1.80 (19H, m, $C_{10}H_{19}$), 1.98 (1H, t, SH), 3.23 (2H, d, CH_2), and 4.68 (1H, m, CH). Found: C, 62.48; H, 9.70%. Calculated for $C_{12}H_{22}O_2S$: C, 62.56; H, 9.62%. To a stirred solution of (-)-isoborneol (0.32 mol) and pyridine (0.45 mol) in dry ether (250 mL) was added a solution of crotonyl chloride (0.39 mol) in ether (80 mL) at room temperature. After stirring for 4 h, the reaction mixture was shaken twice with 50 mL of 10% sodium carbonate solution. Distillation of organic layer gave (-)-isobornyl crotonate (3). Yield: 48-53%. bp 100-103°C (3 mmHg). $[\alpha]_D^{25}$ -54.6° (c = 1, CH_3OH). IR (neat, cm^{-1}): 1720 (C=O), 1660 (C=C), and 1190 (ester). NMR ($CDCl_3$): δ = 0.72-1.73 (17H, m, $C_{10}H_{16}$), 1.84 (3H, d, $OCOCH_3$), 4.58 (1H, t, CH), 5.63 (1H, d, $CH{=}CHCH_3$), and 5.74 (1H, m, $CH{=}CHCH_3$). MS (M^+): 220.

Reaction of 1 with Crotonic Acid (4), Methyl Crotonate (5), and α-Methylstyrene (6)

Typical procedure was as follows. An equimolar mixture of 4 (60 mmol) and 1 in benzene (10 mL) containing 2,2'-azobisisobutyronitrile (AIBN) (1.2 mmol) was heated at 70°C for 8.5 h under a nitrogen atmosphere, and then the solvent and the unreacted components were distilled under reduced pressure. After the residue was treated with lithium aluminum hydride ($LiAlH_4$) in dry ether at room temperature for 12 h, dilute sulfuric acid was added to decompose the excess of hydride. The organic materials were treated with silica gel thin-layer chromatography (TLC) to yield 73% of 3-β-hydroxyethylthio-1-butanol (9). bp 125-126°C (3 mmHg). IR (neat, cm^{-1}): 3370-3330 (OH); NMR ($CDCl_3$): δ = 1.32 (3H, d, CH_3), 1.75 (2H, q, CH_2), 2.70 (2H, t, CH_2O), 3.01 (1H, m, CH), and 3.73 (4H, t, CH_2); MS (M^+): 150.

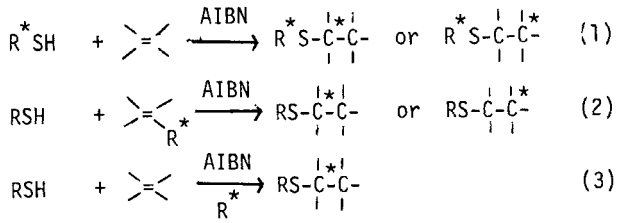
1-β-Hydroxyethylthio-2-phenylpropane (10). IR (neat, cm^{-1}) 3350-3400 (OH), 2980 (CH_3), and 760 (C–S); NMR ($CDCl_3$): δ = 1.37 (3H, d, CH_3), 2.67-3.08 (5H, m, CH_2, CH), 3.50 (2H, t, CH_2O), and 7.15 (5H, s, C_6H_5). Found: C, 67.29; H, 8.22%. Calculated for $C_{11}H_{16}OS$: C, 67.30; H, 8.20%.

Reaction of Thiolacetic Acid (13) with 3

An equimolar mixture of 13 (80 mmol) and 3 containing AIBN (0.2 g) was heated in a degassed ampule at 70°C for 24 h, followed by treatment with $LiAlH_4$ and dilute sulfuric acid. The resulting solution was extracted twice with ether. The combined organic materials were dried over sodium sulfate and distilled under reduced pressure to give 40% of 3-mercapto-1-butanol (14), which was further purified by means of column chromatography until no other impurities were detected. bp 85-87°C (17 mmHg). IR (neat, cm^{-1}): 3680-3320 (OH), and 2560 (SH); NMR ($CDCl_3$) δ = 1.37 (3H, d, CH_3), 1.50 (1H, d, HS), 1.80 (2H, m, CH_2), 3.09 (1H, m, CH), and 3.75 (2H, t, CH_2O). MS (M^+): 106.

RESULTS AND DISCUSSION

Three different types of asymmetric inductions in the free radical additions of thiols to olefins were conceivable: (1) the addition of a chiral group-containing thiol to a prochiral olefin, (2) the addition of an achiral thiol to an olefin-bearing chiral group, and (3) the addition of an achiral thiol to a prochiral olefin in the presence of a chiral substance. In every case we have been successful in getting optically active addition products after the removal of a chiral group. Type 3, which has not been previously mentioned in this article, was described



(1)

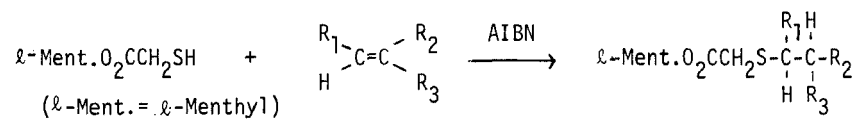
(2)

(3)

R^*: chiral group or substrate.

in an earlier article [8]. All the reactions described below were found to be completely inhibited by the addition of a small amount of hydroquinone, thus indicating that the reactions proceed via a radical process.

We first give experimental evidence of enantioface differentiation in the addition of a chiral group-containing thiol to a prochiral olefin (Type 1). The reactions of a chiral thiol 1 with such prochiral



(ℓ-Ment. = ℓ-Menthyl)

1

4: $R_1=CH_3$, $R_2=H$, $R_3=CO_2H$

5: $R_1=CH_3$, $R_2=H$, $R_3=CO_2CH_3$

6: $R_1=H$, $R_2=CH_3$, $R_3=C_6H_5$

7: $R_1=R_3=C_6H_5$, $R_2=H$

8: $R_1=C_2H_5$, $R_2=R_3=CH_3$

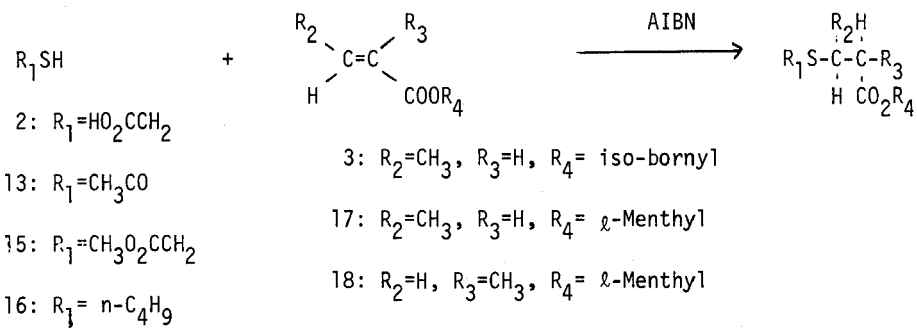
9: $R_1=CH_3$, $R_2=H$, $R_4=CH_2OH$

10: $R_1=H$, $R_2=CH_3$, $R_4=C_6H_5$

11: $R_1=R_4=C_6H_5$, $R_2=H$

12: $R_1=C_2H_5$, $R_2=R_4=CH_3$

olefins as 4-8 using AIBN as a radical initiator, followed by treatment with $LiAlH_4$, gave the corresponding hydroxysulfides 9-12 in fairly good yields (Eq. 4). Table 1 summarizes values of optical rotation of the products together with the previous data [10], indicating that these sulfides are definitely optically active. Unfortunately, however, these sulfides are new optically active compounds and their absolute configurations have not yet been determined. The e.e.% of 9 was calculated on the basis of the rotation of -3.09° for (-)-9 of 15 e.e.% which was determined with the use of a shift reagent as described in a later section. The e.e.% of 10 was not determined successfully even by the use of such chiral shift reagents as tris[3-(trifluoromethylhydroxymethylene)-d-camphorate] europium(III) and tris[3-(heptafluoropropylhydroxymethylene)-d-camphorate] europium(III). It is interesting to note that in the reaction of 1 with 6, the chirality is induced at α-olefinic carbon atom of 6, while in other reactions the chiral centers of the products are located at the carbon atoms attached to the sulfide group. These findings indicate that asymmetric induction could occur both at the addition step of thiyl radical to olefin and at the hydrogen abstraction step of the growing radical from thiol.



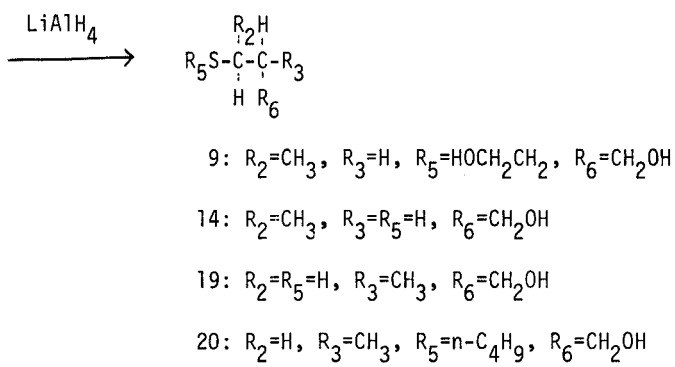


TABLE 1. The Reaction of 1 with Olefins[a]

Olefin (80 mmol)	Temperature (°C)	Solvent (mL)	Time (h)	Product	Yield (%)	$[\alpha]_D^{25}$ (c, solvent)	e.e. (%)	Ref.
4	70	Benzene (10)	8.5	9	73	-0.68 (18.6, $CHCl_3$)	4.7	This work
4	70	Benzene (10)	7	9	70	-0.72 (24.3, $CHCl_3$)	4.9	This work
5	70	Benzene (10)	7.5	9	82	-0.78 (34.3, $CHCl_3$)	5.4	This work
5	50	Benzene (10)	14	9	84	-0.55 (41.8, $CHCl_3$)	3.8	This work
6	70	Benzene (10)	15	10	60	+0.41 (15.7, $CHCl_3$)[b]	-	This work
7	60	Benzene (250)	6	11	63	+0.63 (9.4, $CHCl_3$)	-	10
8	60	None	6	12	87	+0.20 (18.4, MeOH)	-	10

[a]An equimolar amount of the reactants was taken.
[b]The reaction was carried out in a degassed ampule and the optical rotation was determined at 400 nm by means of ORD.

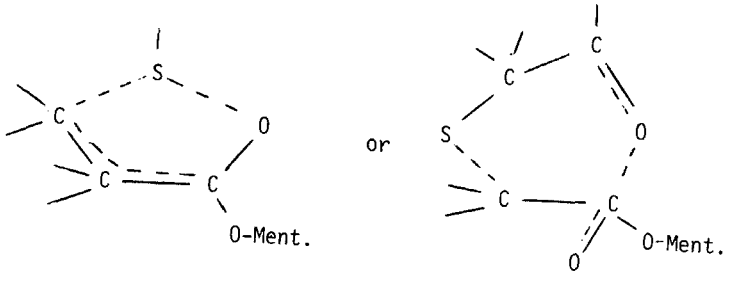
TABLE 2. The Reactions of Achiral Thiols with 3, 17, and 18[a]

Thiol (mmol)	Olefin	Temperature (°C)	Time (h)	Product	Yield (%)	$[\alpha]_D^{25}$ (c, $CHCl_3$)	e.e. (%)	Ref.
2 (80)	17	70	10	9	78	-3.09 (37.0)	15	9
13 (80)	17	70	11	14	70	+3.49 (4.4)	24	9
13 (70)	18	50	10	19	55	+1.70 (1.9)	-	11
13 (100)	3	70	24	14	40	-1.35 (9.1)	19	This work
15 (80)	17	70	10	9	81	-2.76 (36.5)	13	9
16 (70)	18	60	8	20	30	-0.16 (1.8)	-	11

[a]An equimolar amount of the reactants was taken and the reaction was carried out in a degassed ampule.

Diastereoface differentiation in the addition of an achiral thiol to an olefin-bearing chiral group (Type 2) has also been successful in the reactions of a few achiral thiols 2, 13, 15, or 16 with 17, 18, or 3 with the use of AIBN as a radical initiator followed by the treatment with $LiAlH_4$ to give optically active products 9, 14, 19, and 20 (Eq. 5 and Table 2). The e.e.% of 9 and 14 were determined successfully by the use of tris[3-(heptafluoropropylhydroxymethylene)-d-camphorate] europium(III); i.e., 9 and 14 were treated with acetic anhydride in pyridine to give their diacetyl compounds whose methyl proton ($-OCOCH_3$) showed distinct differences with an addition of the shift reagent. On the other hand, the e.e.% of products 19 and 20 were not determined successfully. Table 2 reveals again that asymmetric induction occurred either at the addition step of thiol radical to olefin (the reactions with 17 and 3) or at the hydrogen abstraction step of the growing radical from thiol (the reactions with 18).

It is difficult to deduce a meaningful mechanisms for the above asymmetric induction. However, it can be pointed out that the distance between the chiral center and the reaction center should be rather large; namely, 6 or 7 atoms are involved in the Type 1 addition (Eq. 4) and 4 or 5 atoms in the Type 2 addition (Eq. 5). Hence the differentiation is not controlled simply by a steric factor. One possible assumption is that a cyclic or bridged intermediate can be formed to stabilize the transition state of the reaction. A similar bridged intermediate with the assistance of the carbonyl group of the attacking thiyl radical was assumed in the radical addition of 9 to 2-chloro-4-butylcyclohexene [12]. The stereochemical course of the radical hydrostannation of ℓ-menthyl crotonate was also taken into account by considering cisoid conformations which would allow stabilizations of the transition state by electrostatic interaction [13]. We wish to believe that similar stabilization would occur at the transition state of the above addition reaction, for example, as shown in Eq. 6, although a definite explanation of the transition state has not been offered for the addition reactions treated in this work.



It is noted that (+)-14 was obtained in the reaction of 13 with 17 while (-)-14 was obtained with 3, where the ℓ-menthyl group in 17 has an opposite steric hindrance compared with the isobornyl group in 3. This might be caused by the steric effect of the chiral group to the bridged intermediate. It is also conceivable that in the reactions of 1 with 6 and of 18 with 13, hydrogen abstraction would occur at a sterically less hindered enantioface of the sp^2 radical exerted by a steric effect of the menthyl group to the bridged intermediate.

We cannot present a more meaningful explanation for our novel asymmetric induction. However, we consider our observations to demonstrate a valuable concept toward developing a new type of asymmetric induction via a free radical process.

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