propriate model for the substrate of enoyl-CoA hydratase (EC 4.2.1.17), one of the enzymes that catalyze syn eliminations. In addition, a thorough investigation on elimination reactions of the unlabeled 3-acetoxy thioester has been reported.[6] Fedor concluded that this base-catalyzed elimination of acetic acid is either E2 or E1cB with fast reaction of the carbanion.

NMR studies showed that our synthesis of **1** was stereospecific.[7] Later ^{1}H NMR investigations at 300 MHz, where the diastereotopic protons at C-2 were separated by 0.18 ppm, showed that the synthesis of **1** also produced 2.9% of the nondeuterated acetoxy thioester.

Our preliminary experiments on the stereochemistry of reaction 1 have shown some interesting results. Reaction of **1** at 25 °C in 3:1 EtOH/H_2O with 1.69 M KOH (10% excess) produced *S-tert*-butyl (*E*)-2-butenethioate (**2**) in 70–85% yield.[8] NMR analysis of nondeuterated **2** ($CDCl_3$) showed peaks at δ 6.8 (m, 1, C_3H), 5.97 (br d, 1, C_2H), 1.84 (dd, 3), and 1.5 (s, 9); UV_{max} was 262 nm (EtOH/H_2O, ϵ 6280). Compounds **1** and **2** did not undergo significant proton exchange with protonated or deuterated solvents under reaction conditions. The *Z*-alkene, synthesized by hydrogenation of tetrolic acid and esterification in the usual manner,[7] was formed in only 1% yield from reaction (1) and was stable under reaction conditions. A k_H/k_D value of 5.2 ± 0.1 was obtained through comparative (UV) second-order rate measurements on the diprotonated and dideuterated thioesters in EtOH/H_2O (3:1).[9]

Compound **2** was purified by preparative GC ($^3/_8$ in. × 8-ft 15% Carbowax 20 M column) and the vinyl protons were integrated by NMR. Multiple integrations in two separate experiments gave an average isotopic composition of 57.0 ± 1.2% ^{1}H and 43.0 ± 1.2% ^{2}H at C-2. After correction for the isotope effect, we find the stereochemical preference for the undeuterated substrate to be 86% anti and 14% syn elimination. The same results were obtained when the reaction was run to 50% completion. That this is the result of a definite stereochemical preference for anti elimination is demonstrated by the fact that the deuteron of **1** is eliminated 1.3 times faster than the proton. If a secondary isotope effect of 1.15 pertains in the rate of the dideuterated thioester,[10] the stereochemical preference is 85% anti/15% syn.

Reaction of **1** with LiOH, rather than KOH, in EtOH/H_2O gave virtually the same stereochemistry. However, reaction of **1** at 25 °C in hexane with lithium *tert*-butoxide (0.35 M, 20% excess) resulted in a much greater preference for syn elimination. The *t*-BuOLi/hexane reaction gave 85+% recovered yields of **2**. Control experiments showed that isomerization of the *Z*-alkene and proton exchange on **2** were negligible. Multiple NMR integrations on **2** from duplicate reactions gave an average isotopic composition of 13.0 ± 1.2% ^{1}H and 87.0 ± 1.3% ^{2}H at C-2. Kinetic isotope effects are relatively insensitive to base strength and association.[3,11] With correction for an isotope effect of 5.2, the values expected for the parent unlabeled β-acetoxy thioester are 44% anti and 56% syn elimination.

The 15% syn elimination from **1** in EtOH/H_2O is the largest deviation from the anti rule ever observed with base-catalyzed 1,2-elimination reactions on neutral acyclic compounds in a non-ion pairing medium. Such compounds rarely produce more than 5% syn elimination under ion-dissociating conditions; reaction of *t*-BuOK/Me_2SO with 5-fluoro[6-$^2H_1$]decane gave 12% syn elimination, the greatest amount observed heretofore.[12] Fluoride is a poor leaving group, and the transition state should have a good deal of carbanionic character. Most activated acyclic E2 eliminations for which stereochemical data are available have used phenyl or halogen activating groups. In contrast to our results, such compounds exhibit a diminished propensity for syn elimination.[3] In our reactions, which are at the E2–E1cB borderline, the transition states probably have a large amount of carbanion character and a small amount of C=C character. As expected, ion pairing with *t*-BuOLi/hexane favors a syn elimination pathway, so that syn and anti elimination occur with nearly equal facility.

That syn and anti stereochemistry compete effectively in base-catalyzed elimination reactions of the acetoxy thioester **1** may be of some biochemical significance. It now seems reasonable that enoyl-CoA hydratase and other enzymes catalyzing syn eliminations on acyclic substrates may do so for reasons of mechanistic efficiency. We are continuing to investigate the importance of substrate acidity, base strength, and leaving group on these reactions.

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Registry No. (*R,R*)-**1**, 86195-04-2; (*S,S*)-**1**, 86195-05-3; (*E*)-**2**, 86146-56-7; deuterium, 7782-39-0.

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Optical Resolution of 3-Methylcycloalkanones and 5-Methyl-γ-butyrolactone by Complexation with Optically Active 1,6-Bis(*o*-halophenyl)-1,6-diphenylhexa-2,4-diyne-1,6-diol

Fumio Toda* and Koichi Tanaka

Department of Chemistry, Faculty of Engineering Ehime University, Matsuyama 790, Japan

Tetsuo Omata, Kazuyoshi Nakamura, and Tokio Ōshima

Central Research Laboratory, Ube Industries, Ltd. Ube 755, Japan

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Optical resolution of guest molecules utilizing the inclusion phenomena in a host has been studied by several research groups.[1] Efficiency of the resolution, however, is not high except for some special cases involving the resolution of 2-chlorooctane by urea[1a] and of phosphinates[1d] and sulfinates[1e] by cyclodextrin. Recently, Cram and co-workers succeeded in resolving amino acids and amines as their salts quite efficiently by using the inclusion phenomena in optically active crown ethers.[1g-i] Nonetheless, an optically active host molecule that can resolve a neutral guest molecule efficiently has yet to be prepared. We now report optical resolution of 3-methylcyclohexanone (**3**), 3-methylcyclopentanone (**4**), and 5-methyl-γ-butyrolactone (**5**) by complexation with optically active 1,6-bis(*o*-halophenyl)-1,6-diphenylhexa-2,4-diyne-1,6-diol (**2b–d**).

Previously, we have reported that 1,1,6,6-tetraphenylhexa-2,4-diyne-1,6-diol (**2a**) forms 1:2 crystalline complexes with various guest molecules.[2a,c] It was also confirmed by an X-ray structural

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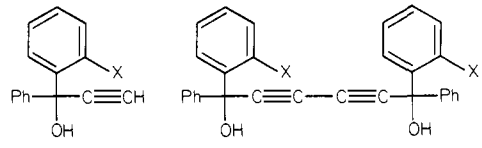
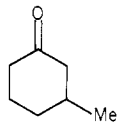


1

2

2a, X = H 2c, X = Cl
2b, X = F 2d, X = Br



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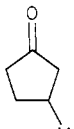

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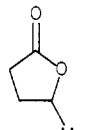

5

study of the 1:2 complex of **2a** and acetone that a hydrogen bond between OH of **2a** and acetone forces the latter in the vicinity of the saturated carbon of the former in the complex.[2b,c] These data suggest the potential for optical resolution of a guest molecule by complexing with optically active **2b–d**. Oxidative coupling of 100% optically pure 1-(*o*-halophenyl)-1-phenylpropyn-1-ol (**1b–d**), which had been obtained by previously reported resolution method,[3] gave in almost 100% ee[4] **2b** (mp 166–168 °C, $[\alpha]_D$ 47.7°[4]), **2c** (mp 127–129 °C, $[\alpha]_D$ 122°), and **2d** (mp 139–141 °C, $[\alpha]_D$ 129°), respectively. By this method, both the *d*- and *l*-enantiomers of **2b–d** were prepared in 100% ee. In all cases of the optical resolution, 100% ee **2b–d** were used.

When a solution of *l*-**2c** (19.2 g, 39.8 mmol) and *dl*-**3** (17.8 g, 159 mmol) in ether–petroleum ether (1:1, 100 mL) was kept at room temperature for 6 h, a 1:2 complex of *l*-**2c** and *d*-**3** (25.5 g, 91%,[5] $[\alpha]_D$ −85.8°) was obtained as colorless prisms. Upon heating the complex, 28% ee *d*-**3** (8.0 g, 90%,[5] $[\alpha]_D$ +4.0° ($CHCl_3$)) was obtained by distillation.[6] The remaining *l*-**2c** was 100% optically pure. Two recrystallization of the 1:2 complex of *l*-**2c** and the 28% ee *d*-**3** (25.5 g) from ether–petroleum ether (1:1, each 80 mL) gave the complex (11.6 g, 41%, $[\alpha]_D$ −84.0°) that, on distillation, gave 66% ee *d*-**3** (3.5 g, 39.3%, $[\alpha]_D$ +9.5° ($CHCl_3$)). When the same recrystallization was repeated twice for the complex prepared from *l*-**2c** and the 66% ee *d*-**3** (3.7 g), the 1:2 complex of *l*-**2c** and 100% ee *d*-**3** (4.1 g, 15%, mp 78–79 °C, $[\alpha]_D$ −71.7°) was obtained. By further recrystallization, the $[\alpha]_D$ value of the complex did not change. Upon heating the complex, 100% ee *d*-**3** (1.16 g, 13%, $[\alpha]_D$ +14.4° ($CHCl_3$), lit.[7] +14.4° ($CHCl_3$, *c* 0.01)) was obtained after distillation.

This resolution method was not effective for 2-methylcyclohexanone and only the 2% ee *d*-enantiomer was obtained in 95% yield by a single complexation with *l*-**2c**. This suggests that the distance between the chiral center and the carbonyl group in the guest molecule is crucial to the efficiency of resolution. In support of this, **4** and **5** were resolved quite efficiently by this method. Complexation of *l*-**2c** (7.7 g, 16 mmol) and *dl*-**4** (6.3 g, 64 mmol) in ether–petroleum ether (1:1, 50 mL) at room temperature for 6 h gave the 1:1 complex of *l*-**2c** and *l*-**4** (9.4 g, 86%, $[\alpha]_D$ −20.2°). Seven recrystallizations of the above complex from ether–petroleum ether (1:1, each 30 mL) gave the 1:2 complex of *l*-**2c** and 100% ee *l*-**3** (0.87 g, 8%, mp 61–63 °C, $[\alpha]_D$ −126°), the $[\alpha]_D$ value of which did not change by further recrystallization. When the complex was heated, 100% ee *l*-**4** (0.19 g, 6%, $[\alpha]_D$ −148°) was obtained by distillation.

Similar complexation of *l*-**2c** (13.4 g, 27.7 mmol) and *dl*-**5** (11.1 g, 111 mmol) gave the 1:2 complex of *l*-**2c** and *l*-**5** (18.5 g, 98%, $[\alpha]_D$ +5.1°). Recrystallization of the complex from ether–petroleum ether (1:1, each 50 mL) was repeated 12 times to give the 1:2 complex of *l*-**2c** and 100% ee *d*-**5** (0.95 g, 5%, mp 94–95 °C, $[\alpha]_D$ −81.3°). Heating of the complex resulted in 100% ee *d*-**5** (0.25 g, 4.5%, $[\alpha]_D$ +30.1°, lit.[8] +33.3° (neat)).

When *d*-**2c** was used instead of *l*-**2c** for the resolution of **3**, **4**, and **5**, the other enantiomers *l*-**3**, *d*-**4**, and *l*-**5** were obtained, respectively, in almost the same yields as those by *l*-**2c**. For example, when a solution of *d*-**2c** (8.1 g, 16.7 mmol) and *dl*-**5** (6.7 g, 67 mmol) in ether–petroleum ether (1:1, 100 mL) was kept at room temperature for 6 h, a 1:2 complex of *d*-**2c** and *l*-**5** (11.2 g, 98%, $[\alpha]_D$ +88.8°) crystallized out, which on distillation gave 17% ee *l*-**5** (3.15 g, 94%, $[\alpha]_D$ −5.2°). Recrystallization of the complex from ether–petroleum ether (1:1, each 30 mL) was repeated 12 times to give the 1:2 complex of *d*-**2c** and 100% ee *l*-**5** (0.69 g, 6%, mp 93–95 °C, $[\alpha]_D$ +81.3°). By heating the complex, 100% ee *l*-**5** (0.17 g, 5%, $[\alpha]_D$ −30.1°) distilled out.

Although **2d** showed almost the same efficiency as did **2c** for the resolution, **2b** was much less effective. One complexation of *dl*-**5** with *l*-**2d** followed by distillation gave 19% ee *d*-**5** (95%), even though the same treatment of *dl*-**5** with *l*-**2b** gave *dl*-**5** (87%). When recrystallization of the 1:2 complex of *l*-**2d** and 19% ee *d*-**5** from ether–petroleum ether (1:1) was repeated 12 times, 89% ee *d*-**5** (11%) was obtained after distillation.

The quite efficient optical resolution by the complexation method is probably due to a favorable packing of host and guest molecules in the crystal. The channel formed by optically active **2** includes one enantiomer of a guest selectively and results in more stable complex rather than to include the other enantiomer. X-ray structural study of the complex of *l*-**2c** and *d*-**3** is in progress.

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Crystal and Molecular Structures of 2,11-Dithia- and 1,3,10,12-Tetrathia[3.3](2,6)pyridinophanes

George R. Newkome,* Sebastiano Pappalardo,† and Frank R. Fronczek

Department of Chemistry, Louisiana State University Baton Rouge, Louisiana 70803

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The conformational aspects of 2,11-dithia[3.3]metacyclophanes, prepared as precursors for the corresponding [2.2]metacyclophanes and/or [2.2]metacyclophane-1,9-dienes, have been well studied[1] via the convenient ^1H NMR spectral probes present in the form of the "internal" proton(s) or substituents. Conversely, relatively little is known about the stereochemistry of the structurally related [3.3](2,6)pyridinophanes, which lack these probes. Initial ^1H NMR studies on pyridinophanes **1** and **2** suggested a rapid syn–anti isomerization in bis(sulfide) **1**;[2a] while in tetrasulfide **2**, conjugative factors have been proposed to play a role in raising the energy barrier to ring inversion.[3] Moreover in solution

†On leave from the Istituto Dipartimentale di Chimica e Chimica Industriale, Universita di Catania, Viale A. Doria 6, Catania, Italy, 1982.

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