3828 © 1982 The Chemical Society of Japan Bull. Chem. Soc. Jpn., 55, 3828—3830 (1982) [Vol. 55, No. 12

Optical Resolution of 2,2′,6,6′-Tetrafluorobiphenyl-3,3′-dicarboxylic Acid

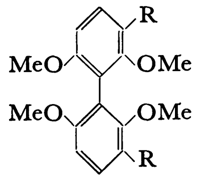
Noriko Hasaka, Masayoshi Okigawa, Isao Kouno, and Nobusuke Kawano*
Faculty of Pharmaceutical Sciences, Nagasaki University, Bunkyomachi, Nagasaki 852

(Received April 16, 1982)

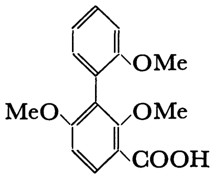
Optically active (−)- and (+)-2,2′,6,6′-tetrafluorobiphenyl-3,3′-dicarboxylic acids were obtained through brucine salts. The half-life times for racemization of their dimethyl esters were estimated at various temperatures and the activation energy was calculated to be 25.6 kcal/mol.

Recently, the optical resolution of 2,2′,6,6′-tetramethoxybiphenyl compounds (**1** and **2**), 2,2′,6-trimethoxybiphenyl-3-carboxylic acid (**3**), and 2,2′-difluoro-6,6′-dimethoxybiphenyl-3-carboxylic acid (**4**) were reported.[1] These results disclosed the erroneous findings reported by Adams and co-wokers[2] and stimulated us to attempt the optical resolution of 2,2′,6,6′-tetrafluorobiphenyl-3,3′-dicarboxylic acid (**5**), although Adams and co-workers reported[3] that 2,2′,6,6′-tetrafluoro-5,5′-dichlorobiphenyl-3,3′-dicarboxylic acid (**6**) was nonresolvable. The activation energy for racemization of the compound **5** should be less than that of the compounds, **1** and **4** because of the smaller van der Waals radius of fluorine atom than that of oxygen.

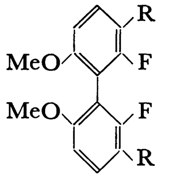
Racemic **5** was obtained from *m*-difluorobenzene by a synthetic route shown in Scheme 1 although another route was formerly reported.[4] The optical resolution of **5** was achieved through brucine salts. Fortunately, two kinds of brucine salts were obtained in the course of the resolution. The first salt, mp 151—156 °C, gave (−)-acid, mp 243—245°C, $[\alpha]_D^{24}$ −35.9° (ethanol) and the second salt, mp 169—179 °C, gave (+)-acid, mp 241—244 °C, $[\alpha]_D^{24}$ +36.2° (ethanol). Their dimethyl esters were also optically active and showed $[\alpha]_D^{24}$ −33.5° (dioxane) and +34.0° (dioxane), respectively. In the preceding paper[1] the optical purities of active esters were estimated from ^{1}H NMR spectra taken with use of a chiral NMR-shift reagent (CSR), tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium(III).[5] However, the racemic ester of **5** showed only one set of signals even in the presence of a large amount of the same CSR. Therefore, NMR-shift reagents were not useful for the estimation of the optical purities of the active esters of **5**.



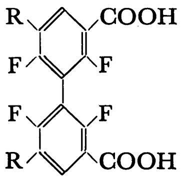
1 R=COOH
2 R=NH_2



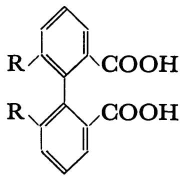
3



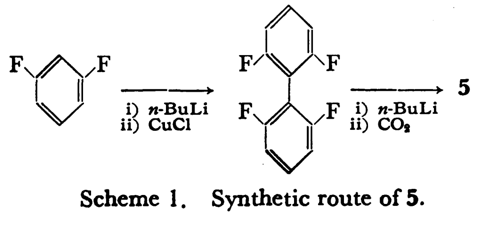
4 R=COOH
9 R=H



5 R=H
6 R=Cl



7 R=F
8 R=OMe



Scheme 1. Synthetic route of **5**.

Racemization experiments were performed with use of both the (−)- and (+)-dimethyl esters and the results obtained are shown in Tables 1 and 2. The activation energy for racemization of these active esters was first determined graphically; 25.9 kcal/mol from the (−)-ester (Table 1) and 25.7 kcal/mol from the (+)-ester (Table 2). Calculations by the least squares method at 95% confidence limit gave 25.4±1.0 kcal/mol from the (−)-ester and 25.8±0.8 kcal/mol from the (+)-ester. The mean of these values is 25.6 kcal/mol, and this value is 13.8 kcal/mol less than the activation energy of the optically active ester of **4** (39.4 kcal/mol in a 2-phenylethanol solution),[1] corresponding to the structural difference between **4** and **5**, fluorine atoms instead of methoxyl groups at 6- and 6′-positions.

Table 1. Racemization data[a] of (−)-dimethyl ester of **5**

Temp/°C	Time/min	α_{546}^{20}/°	log *k*	Half-life time/min
73.9±0.2	360	−0.0495	−4.611	469.5
79.6±0.1	240	−0.045	−4.363	267.0
88.7±0.2	90.75	−0.047	−3.957	104.8
97.1±0.1	60	−0.035	−3.614	47.5

a) A solution of 30.0 mg of (−)-ester in 10.0 ml of dioxane was used. Initial rotation: α_{546}^{20} −0.084° (l=10.00 cm).

Table 2. Racemization data[a] of (+)-dimethyl ester of **5**

Temp/°C	Time/min	α_{546}^{20}/°	log *k*	Half-life time/min
75.3±0.1	300	+0.082	−4.551	411.0
80.9±0.1	180	+0.078	−4.288	224.3
89.0±0.1	90	+0.073	−3.938	100.3
96.9±0.1	60	+0.056	−3.608	46.9

a) A solution of 41.0 mg of (+)-ester in 10.0 ml of dioxane was used. Initial rotation: α_{546}^{20}+0.136°(l=10.00 cm).

A similar structural difference can be seen in two compounds, 2,2′-difluorobiphenyl-6,6′-dicarboxylic acid (**7**) and 2,2′-dimethoxybiphenyl-6,6′-dicarboxylic acid (**8**), reported by Adams and co-workers.[6] Racemization data of these compounds observed by them are as follows: The complete racemization time of **7** was about 2 h in boiling ethanol or 10 min in boiling acetic anhydride, whereas the half-life period of **8** was 78 min in boiling glacial acetic acid or about 60 h in boiling ethanol. Afterwards, the racemization of **8** was extensively studied in various solvents and the ΔH^{*} in dioxane has been reported[7] as 25.15±0.07 kcal/mol. This value of **8** should be larger than that of **7**. However, the energy difference between **7** and **8** is only a few kcal/mol at most. This is much less than the former difference of 13.8 kcal/mol between **4** and **5**. The reasons considered are as follows: a) The electronic effects of carboxyl groups in **4** and **5**, b) the use of a different solvent (2-phenylethanol) in the case of **4**, and c) in **4** and **5**, racemization requires the passage of MeO (**4**) and F (**5**) groups past F groups, whereas in **7** and **8**, F (**7**) and MeO (**8**) groups must pass COOH groups.

In order to investigate the molecular chirality of **4** without buttressing effects ^{1}H NMR spectra of 2,2'-difluoro-6,6'-dimethoxybiphenyl (**9**) were taken with use[8,9] of the CSR. When two molar ratio of the CSR was added, two methyl signals were observed with a chemical shift difference of 2.5 Hz, indicating that **9** is chiral at room temperature on the NMR time scale. This observation means that F and MeO groups at *ortho*-position of biphenyl compounds are large enough to restrict the rotation without buttressing effects. The lower limit of the rotational barrier of **9** may be estimated to be about 16 kcal/mol from the Eyring equation.[10] Adams' method[11] of predicting the resolvability of chiral biphenyls should be partly revised since there have been some reports[12] concerning the effective van der Waals radii of these atoms and groups.

Experimental

All melting points are uncorrected. Optical rotations were measured with a Nihon-Bunko (JASCO) DIP-181 polarimeter. UV and IR spectra were recorded with a Hitachi 323 recording spectrometer and a JASCO IRA-2 grating infrared spectrophotometer respectively. ^{1}H NMR spectra were recorded with a JEOL PS-100 instrument using TMS as internal reference. Mass spectra were obtained from a JEOL JMS-01SG double-focus instrument.

2,2',6,6'-Tetrafluorobiphenyl. *m*-Difluorobenzene (2.0 g) was dissolved in anhydrous tetrahydrofuran (THF, 50 ml) and kept at −70 °C in a Dry Ice and methanol mixture. To the cooled and stirred solution was added dropwise 15% butyllithium hexane solution (12.5 ml) during 15 min. Stirring was continued for a further 3 h period at the same temperature and then anhydrous $CuCl_2$ (2.9 g) was added. After the mixture was stirred for 2 h the temperature slowly rose to room temperature during 1 h. Stirring was continued for 5 h at room temperature. The reaction mixture was acidified with diluted hydrochloric acid and extracted with diethyl ether. The ether solution was washed with water, dried over $MgSO_4$, and evaporated. The reaction product was purified by column chromatography (silica gel and hexane) to give a product (1.03 g), mp 47.5—48.5 °C from hexane–ether (reported[13] mp 47.5—48.5 °C), UV$_{max}$ (EtOH) 230 (log ε 4.16) and 265 nm (3.24); IR (KBr) 1615, 1459, 1265, 1234, 1004 (C–F), and 990 cm^{-1}; MS *m/z* 226 (M^{+}).

2,2',6,6'-Tetrafluoro-3,3'-bis(methoxycarbonyl)biphenyl. 2,2',6,6'-Tetrafluorobiphenyl (2.5 g) was dissolved in anhydrous THF (70 ml) and kept at −70 °C. To the cooled and stirred solution was added dropwise 15% *n*-BuLi hexane solution (12.0 ml) during 15 min. Stirring was continued for further 6 h at the same temperature and dried CO_2 was introduced to the cooled solution for 2 h. During that time the temperature of the reaction mixture was gradually raised to room temperature. The mixture was acidified with diluted hydrochloric acid and extracted with diethyl ether. The ether solution was washed with water, dried over $MgSO_4$, and evaporated. The reaction products obtained were methylated with diazomethane and purified by column chromatography (silica gel and hexane and then hexane–chloroform) to give colorless needles from hexane–diethyl ether (0.7 g, 18.5% yield), mp 136.5—137.5 °C (reported[4] mp 136—137 °C); UV$_{max}$ (EtOH) 218 (log ε 4.60) and 277 nm (3.45); IR (KBr) 1722 (C=O), 1267, 1216, 1131, and 1007 cm^{-1}; MS *m/z* 342 (M^{+}), 311 (M-OCH$_3$, base peak), 252, 224; ^{1}H NMR ($CDCl_3$) δ 3.96 (6H, s, Me), 7.11 (2H, br. t, *J*=8.1 Hz), 7.90—8.25 (2H, m).

2,2',6,6'-Tetrafluorobiphenyl-3,3'-dicarboxylic Acid (5). The above diester (0.70 g) was hydrolyzed with 8% NaOH solution (20 ml) at 90 °C for 2 h to give colorless acid and recrystallized from diluted ethanol, mp above 295 °C (reported[4] mp 306.5—307.5 °C), (0.61 g, 95% yield); UV$_{max}$ (EtOH) 215 (log ε 4.57) and 274 nm (3.55); IR (KBr) 3433, 2980, 2590, 1710 (C=O), 1607, 1261 (COOH), 1039, and 1010 cm^{-1}; MS *m/z* 314 (M^{+}), 297, 269, and 224.

(−)-2,2',6,6'-Tetrafluorobiphenyl-3,3'-dicarboxylic Acid. Racemic **5** (157 mg, 0.5 mmol) and brucine dihydrate (430 mg, 1.0 mmol) were dissolved in hot ethanol (5 ml) and left to stand overnight. Brucine salt obtained was recrystallized two times from ethanol to afford colorless crystals (35 mg), mp 151—156 °C, which were decomposed with 10% hydrochloric acid and extracted with ether. The ether solution was washed with water, dried over $MgSO_4$, evaporated, and crystallized from ethanol to give optically active acid (8 mg), mp 243—245 °C, $[\alpha]^{24}_{D}$ −35.9° and $[\alpha]^{24}_{546}$ −40.9° (0.32%, EtOH).

(−)-2,2',6,6'-Tetrafluoro-3,3'-bis(methoxycarbonyl)biphenyl. The above (−)-acid (25.8 mg) was methylated with diazomethane to give an optically active ester (27.5 mg), mp 55—58 °C, $[\alpha]^{24}_{D}$ −33.5° and $[\alpha]^{24}_{546}$ −40.4° (0.49%, dioxane); UV$_{max}$ (EtOH) 218 (log ε 4.58) and 277 nm (3.43); IR, MS, and ^{1}H NMR the same with those of racemic dimethyl ester.

(+)-2,2',6,6'-Tetrafluorobiphenyl-3,3'-dicarboxylic Acid. The filtrate separated from the first brucine salt was evaporated to about 3.5 ml and left to stand overnight to give the second salt, which was recrystallized two times from ethanol to afford colorless crystals (98 mg), mp 173—179 °C. The salt was decomposed and the optically active acid obtained was crystallized from ethanol to give colorless crystals (24 mg), mp 241—244 °C, $[\alpha]^{24}_{D}$ +36.2° and $[\alpha]^{24}_{546}$ +41.2° (1.2%, EtOH).

(+)-2,2',6,6'-Tetrafluoro-3,3'-bis(methoxycarbonyl)biphenyl. The above (+)-acid (38 mg) was methylated with diazomethane to give a dimethyl ester (41 mg), mp 56—59 °C, $[\alpha]^{24}_{D}$ +34.0° and $[\alpha]^{24}_{546}$ +40.6° (1.1%, dioxane); UV$_{max}$ (EtOH) 218 (log ε 4.57) and 277 nm (3.42); IR, MS, and ^{1}H NMR the same with those of racemic dimethyl ester.

The authors are grateful to Professor K. Mislow, Princeton University, for his valuable advices and encouragements and Miss H. Kammura and Y. Kawabata for their technical assistance.

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