Pergamon

Tetrahedron, Vol. 53, No. 12, pp. 4179-4184, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00146-4

Unusual Monosubstitution-Monodechlorination Product in the Reaction of 1,8-Dichloroanthraquinone With (*S*)-(-)-2-(Tetrahydropyranyloxy)-1-propanol

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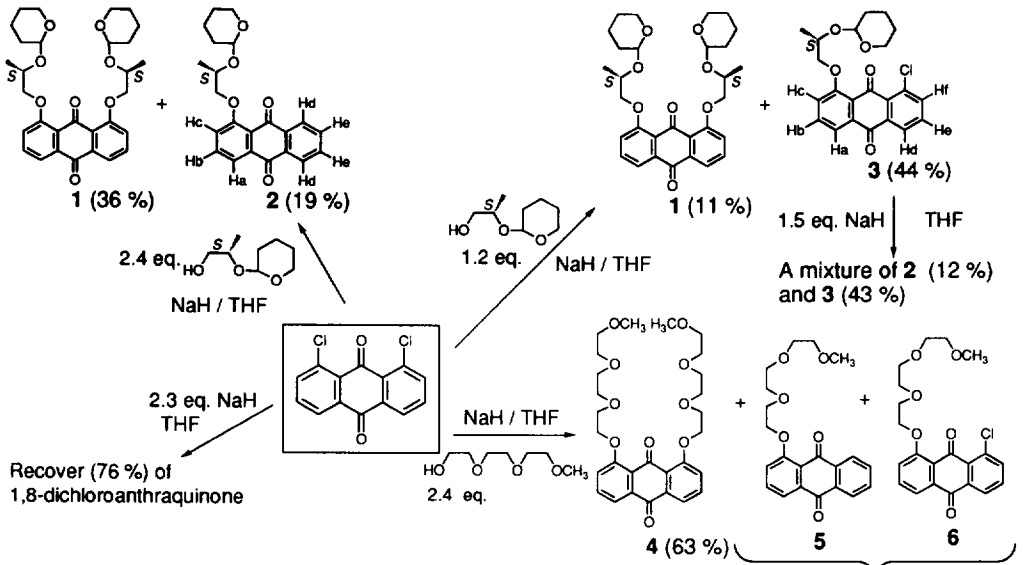
Abstract: Treatment of 1,8-dichloroanthraquinone with (*S*)-(-)-2-(tetrahydropyranyloxy)-1-propanol in the presence of NaH in THF gave monosubstituted-monodechlorinated product **2** and the desired 1,8-disubstituted product **1**. Molecular mechanics calculations and ^{1}H NMR experiments suggest that the tetrahydropyranyl group in the side chain of monosubstituted-monochloro product **3** hinders the second reaction site and the Na^+ cation interacts with the oxygen atoms of the side chain and ketone function allowing the hydride anion access to the second reaction site. © 1997 Elsevier Science Ltd.

Increased attention has been focused on 1,8-disubstituted anthraquinone derivatives in host-guest chemistry. The anthraquinone unit has been used for electrochemical switching in lariat crown ethers and podands.[2] Recently, it has been used to construct the organic superstructure in π-π donor-accepter host-guest systems.[3] In connection with our continuing studies of chiral pyridino-18-crown-6 ligands,[4] we have decided to prepare chiral ligands containing the anthraquinone unit. 1,8-Bis[(*S*)-2-(tetrahydropyranyloxy)propyloxy]anthraquinone (**1**) is required as a starting material for these new chiral crown ethers. We herein report a unique by-product, monosubstituted-monodechlorinated compound **2**, when 1,8-dichloroanthraquinone was treated with (*S*)-(-)-2-(tetrahydropyranyloxy)-1-propanol.

A mixture of 1,8-dichloroanthraquinone (7.2 mmol) and (*S*)-(-)-2-(tetrahydropyranyloxy)-1-propanol [4g] (17.0 mmol) in hot THF (30 mL) was slowly added to a refluxing and vigorously stirred suspension of NaH (22.5 mmol) in THF (10 mL).[5] After separation and purification by silica gel column chromatography ($CHCl_3$ and then $CHCl_3$/EtOH = 50/1), the desired disubstituted product **1** and monosubstituted-monodechlorinated product **2** were obtained in 36 % and 19% yields, respectively (Scheme 1). As far as we can tell, this is the first time a monosubstituted-monodechlorinated product has been observed in alkoxide substitution reactions on 1,8-dichloroanthraquinone. When 1.2 equivalents of (*S*)-(-)-2-(tetrahydropyranyloxy)-1-propanol and 1.3 equivalents of NaH were used for 1 equivalent of 1,8-dichloroanthraquinone, disubstituted product **1** and monosubstituted-monochloro product **3** were obtained in 11% and 44% yields, respectively. The structures of **1**, **2**, and **3** were confirmed by ^{1}H NMR and low and high resolution mass spectrometry and elemental analyses.

It is known that many halogenated aromatic compounds are dechlorinated by various reducing agents such as $LiAlH_4$,[6a-6d] $NaBH_4$[6e] and NaH.[6f] No dechlorinated compounds such as 1-chloroanthraquinone or anthraquinone were observed when 1,8-dichloroanthraquinone was refluxed in THF in the presence of 2.3 equivalents of NaH for 96 h. Only starting 1,8-dichloroanthraquinone was recovered in 76 %. The remainder of the starting material presumably decomposed to polar materials. The brown crude product contained considerable material which did not move on TLC analysis. On



Scheme 1

the other hand, when monosubstituted-monochloro derivative **3** was reacted with 1.5 equivalents of NaH in THF for 40 h, a mixture of 12% of **2** and 43% of **3** was obtained. Delgado et al. reported that treatment of triethylene glycol monomethyl ether, which does not have the bulky tetrahydropyranyloxy group, with NaH and 1,8-dichloroanthraquinone gave only disubstituted product **4** in a 64% yield.[5] We repeated their reaction and obtained **4** in a 63% yield along with an 8% amount of a mixture of monosubstituted-monodechlorinated product **5** and monosubstituted-monochloro product **6** which could not be separated (Scheme 1). These results suggest that, in reactions of 1,8-dichloroanthraquinone with ether-containing alcohols in the presence of NaH, the disubstituted product is formed predominantly when a non-bulky alcohol is employed and a monosubstituted-monodechlorinated by-product is formed when a bulky ether-containing alcohol is used. Further, the results suggest that the dechlorinated product is formed from a monosubstituted-monochloro intermediate. Fang et al. reported that steric factors are important in substitution at position 1 of anthraquinone.[7] We believe that the stereochemistry of the side chain in the monosubstituted-monochloro intermediates is an important factor in the formation of monosubstituted-monodechlorinated products **2** and **5**.

In order to obtain information regarding the stereochemistry of the side chain in monosubstituted-monochloro intermediate **3**, the energies for the most stable structures of the two diastereomers, (3′*S*, 5′*R*) and (3′*S*, 5′*S*), were calculated by molecular mechanics (MM2).[8] Figure 1 shows a molecular model of one of the most stable forms of (3′*S*, 5′*R*)-**3** as a typical example. The tetrahydropyranyl group of the side chain covers the second reaction site and, therefore, attack by the second bulky (*S*)-2-(tetrahydropyranyloxy)-1-propoxy anion is inhibited and dechlorination occurs. However, formation of the monosubstituted-monodechlorinated by-product can not be explained by the steric hindrance at the reaction site. Since dechlorinated compounds are not obtained by treating 1,8-dichloroanthraquinone with NaH, it is possible that the oxygen atoms of the monosubstituted side arm are playing a role in this unusual reaction as explained below.

Gustowski et al. reported that compound **5**, which is prepared from 1-chloroanthraquinone, has the ability to bind alkali metal cations.[9] Lu et al. reported that the crystal structure of the bis-NaI complex of 1,5-bis(2-(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)ethoxy)anthracene-9,10-dione showed that the Na^+ ions are bound by ether oxygen atoms

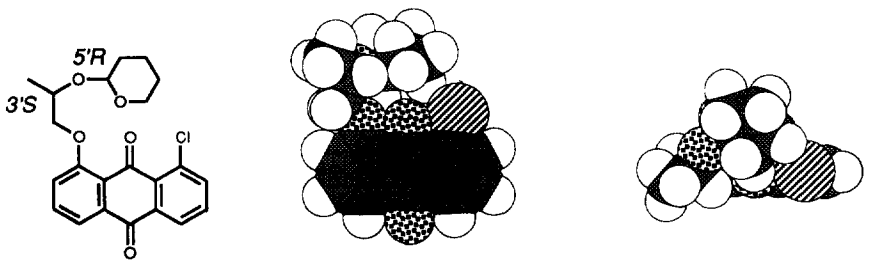


Figure 1. Side and top views of one of the most stable forms of (3'S, 5'*R*)- **3** as obtained by an MM2 calculation using the CAChe program.

of the side arms and the ketone oxygen atoms.[10] If compound **3** can bind a Na^+ ion, it would enhance the reactivity of the counter hydride anion and place it in a position to replace the chloride ion in position 8. A ^1H NMR titration experiment was performed to see whether compound **3** is able to bind a Na^+ ion. Figure 2a shows the ^1H NMR spectral shift changes for the hydrogen atoms of **3** on addition of equimolar amounts of NaH in CD_3OD. There are small shift changes for the signals of the methylene and methine protons next to the oxygen atoms on the side chain and for the aromatic ring protons. The methine proton connected to two oxygen atoms shows the greatest shift. These chemical shift results suggest that compound **3** is binding the Na^+ ion using the ether and ketone oxygen atoms as shown in Figure 2b. From these results, it is reasonable to assume that the counter hydride anion is in a position to replace the chloride ion as shown in Figure 3. After formation of **3**, attack of the second bulky (*S*)-2-(tetrahydropyranyloxy)-1-propoxy anion is inhibited by the tetrahydropyranyl group of the side arm. However, because of the complexation of Na^+ and the small size of the hydride anion, it is able to displace the chloride at position 8 to give monosubstituted-monodechlorinated by-product **2**, as observed. Both steric hindrance and formation of the complex are important in forming the monosubstituted-monodechlorinated compound. Therefore, when 1,8-dichloroanthraquinone was reacted with triethylene glycol monomethyl ether, the non bulky glycol can react on position 8 and only a small amount of monosubstituted-monodechlorinated compound **4** was observed.

It is also possible that the alkoxide of the propanol derivative could act as a reducing agent. Alkoxides are known reducing agents in the Meerwein-Pondorf-Verley reduction.[11] In our case, the reaction of the alkoxide with compound **3** did not produce dechlorinated compound **2**.

In conclusion, we have demonstrated that treatment of 1,8-dichloroanthraquinone with a chiral alcohol containing a bulky group in the presence of NaH gives a monosubstituted-monodechlorinated by-product in addition to the desired disubstituted product. We propose a mechanism for this unique reaction using MM2 calculations and a ^1H NMR titration experiment.

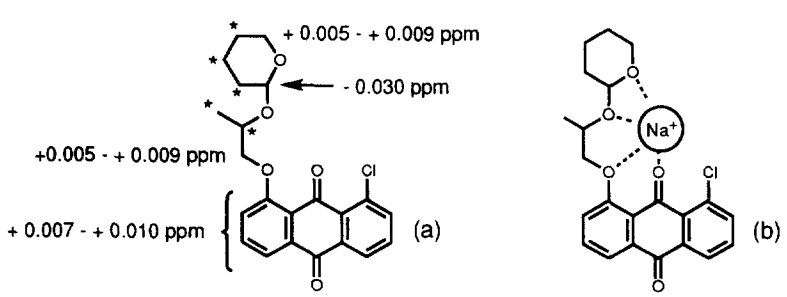


Figure 2. (a) ^1H NMR spectral shift changes of **3** on addition of an equimolar amount of NaH in CD_3OD (298 K). Positive numbers denotes down field shifts. * indicates that protons in those positions shift < ± 0.002 ppm (less than the digital resolution of the NMR). (b) Postulated structure of **3**-Na^+ complex.

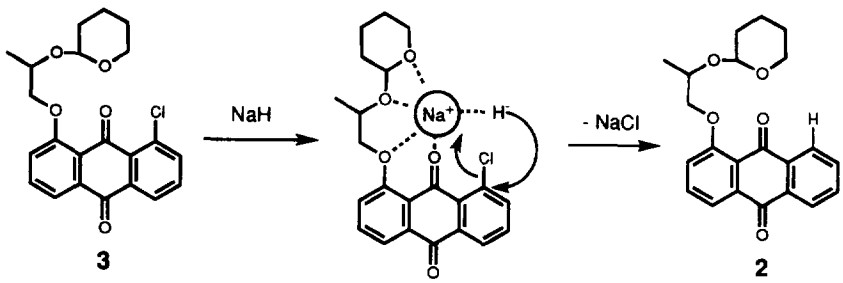


Figure 3. Postulated reaction mechanism to form monosubstituted-monodechlorinated by-product 2.

EXPERIMENTAL SECTION

^{1}H NMR spectra were measured by the Varian Gemini 200 (200 MHz) and VXR-500S (500 MHz) spectrometers. Mass spectra were performed using the JEOL JMS-SX102A spectrometer. Elemental analyses were performed by MHW Laboratories, Phoenix, Arizona. Melting points were taken on the Thomas-Hoover melting point apparatus and are uncorrected. Optical rotation was obtained on a Perkin Elmer model 241 polarimeter.

(-)-1,8-Bis[1,4-dioxa-3-(*S*)-methyl-4-(tetrahydropyranyl)butyl]anthracene-9,10-dione (1) and (+)-1-[(*S*)-2-(Tetrahydropyranyloxy)propyloxy]anthracene-9,10-dione (2). A mixture of 1,8-dichloroanthraquinone (2.0 g, 7.2 mmol) and (*S*)-(-)-2-(tetrahydropyranyloxy)-1-propanol (2.7 g, 17.0 mmol) in 30 mL of hot THF was slowly added to a vigorously stirred and refluxing suspension of NaH (60 % oil dispersion, 0.90 g, 22.5 mmol) in dry THF (10 mL) under an Argon atmosphere. After the reaction mixture was stirred for 40 h, the residual black solution was cooled and then concentrated under reduced pressure. The residue was added to water (50 mL) and extracted with $CHCl_3$ (80 mL x 3). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residual red oil was chromatographed on silica-gel ($CHCl_3$ and then $CHCl_3$/EtOH = 50/1). The first fraction was 1,8-dichloroanthraquinone. The second and the third fractions were **2** (19%) and **1** (36%), respectively. These products have the following properties.

Compound **1**: A yellow oil; ^{1}H NMR: δ 7.82 (t, J = 8.0 Hz, 2H), 7.59 (t, J = 8.0 Hz, 2H), 7.31 (t, J = 8.0 Hz, 2H), 4.82 - 3.40 (m, 12 H), 1.85 - 1.36 (m, 12H), and 1.21 and 1.12 (two doublets, J = 6.4 Hz, total 6H); FABMS (α-monothioglycelol and sodium acetate as matrix): (m/e) 547 (100 %, [M + Na]$^+$), 571 (5 %, [M + H + 2Na]$^+$); HRMS (FAB, α-monothioglycelol and sodium acetate as matrix): (m/e) calcd. for $C_{30}H_{36}O_8Na$ ([M + Na]$^+$) 547.2308, found 547.2312; $[\alpha]_{25}^{D}$ -1.92° (c = 5.68, $CHCl_3$). A satisfactory elemental analysis was obtained for the diol formed from **1**.

Compound **2**: A yellow oil; ^{1}H NMR: δ 8.23 (m, 2H), 7.95 (d, J = 8.0 Hz, 1H), 7.78 (m, 2H), 7.64 (t, J = 8.0 Hz, 1H), 7.36 (t, J = 8.0 Hz, 1H), 4.60 - 3.41 (m, 6H), 1.92 - 1.40 (m, 6H), 1.12 (d, J = 6.4 Hz, 3H); CI MS: (m/e) 224 (100 %, [M - $CH_2CH(CH_3)$O-THP + H]$^+$), 366 (3 %, [M]$^+$); EIMS: (m/e) 224 (100 %, [M - $CH_2CH(CH_3)$O-THP + H]$^+$), 366 (1 %, [M]$^+$); FABMS (α-monothioglycelol and sodium acetate as matrix): (m/e) 389 (100 %, [M + Na]);$^+$FABMS (α-monothioglycelol as matrix): (m/e) 367 (19 %, [M + H]$^+$), 283 (100 %, [M - dihydropyrane + H]$^+$); HRMS (FAB, α-monothioglycelol as matrix): (m/e) calcd. for $C_{22}H_{23}O_5$ [M + H]$^+$ 367.1545, found 367.1552; $[\alpha]_{25}^{D}$ +28.3 (c = 5.41, $CHCl_3$). A satisfactory elemental analysis was obtained for the alcohol formed from **2**.

(-)-1,8-Bis[1,4-dioxa-3-(*S*)-methyl-4-(tetrahydropyranyl)butyl]anthracene-9,10-dione (1) and (-)-1-Chloro-8-[1,4-dioxa-3-(*S*)-methyl-4-(tetrahydropyranyl)butyl]anthracene-9,10-dione (3). (*S*)-(-)-2-(tetrahydropyranyloxy)-1-propanol (0.35 g, 2.16 mmol) in 5 mL of dry THF was slowly added to a suspension of NaH (60 % oil dispersion, 0.092 g, 2.30 mmol) in dry THF (20 mL) at 0 °C under an Argon atmosphere. The mixture was refluxed for 1 h and then stirred for 3 h at rt. After 1,8-dichloroanthraquinone (0.50 g, 1.8 mmol) was added, the solution was stirred under reflux for 40

h. The reaction mixture was treated in the same manner as described above. The reaction mixture was chromatographed on silica-gel column using $CHCl_3$ as the eluent to give disubstituted (**1**) and monosubstituted (**3**) derivatives in 11% and 44% yields, respectively. Compound **3** was a yellow oil; ^{1}H NMR: δ 8.18 (d, J = 7.6 Hz, 1H), 7.85 (d, J = 7.6 Hz, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.65 (t, J = 8.0 Hz, 1H), 7.59 (t, J = 8.0 Hz, 1H), 7.39 and 7.72 (two doublet, J = 8.0 Hz, total 1H), 5.14 (s, 0.6 H), 4.83 (s, 0.4H), 4.43 - 3.97 (m, 4H), 3.60 - 3.47 (m, 1H), 1.82 - 1.56 (m, 6H), 1.39 (d, J = 6.4 Hz, 3H); CIMS: (m/e) 317 (100 %, [M - dihydropyrane]$^+$), 401 (5 %, [M]$^+$); FABMS (α-monothioglycerol as matrix): (m/e) 317 (100 %, [M - dihydropyrane]$^+$), 402 (10 %, [M + H]$^+$); HRMS (FAB, α-monothioglycerol as matrix): (m/e) calcd. for $C_{22}H_{21}O_5{}^{35}Cl$ [M + H]$^+$ 400.1078, found 400.1077 (100 %) and calcd. for $C_{22}H_{21}O_5{}^{37}Cl$ [M + H]$^+$ 402.1048, found 402.1058 (28 %); $[\alpha]_{25}^{D}$ +17.86 (c = 5.07, $CHCl_3$). Anal calcd for $C_{22}H_{21}O_5Cl \cdot 0.8\ H_2O$: C, 63.63; H, 5.49. Found: C, 63.81; H, 5.90.

1,8-Bis(1,3,5,7-tetraoxaundecyl)anthracene-9,10-dione (4), 1-(1,3,5,7-Tetraoxaundecyl)anthracene-9,10-dione (5) and 1-Chloro-8-(1,3,5,7-tetraoxaundecyl)anthracene-9,10-dione (6). According to the procedure described by Delgado. et al.[5], a mixture of 1,8-dichloroanthraquinone (2.00 g, 7.2 mmol) and triethylene glycol monomethyl ether (2.80 g, 17.1 mmol) in hot THF (30 mL) was slowly added to a vigorously stirred and refluxing suspension of NaH (60 % oil dispersion, 0.90 g, 22.5 mmol) in dry THF (10 mL). The reaction mixture was stirred for 21 h, cooled and concentrated under reduced pressure. The residual red oil was purified by column chromatography on silica gel ($CHCl_3$ and then $CHCl_3$/EtOH = 300/1- 10/1 as eluents) to give **4** (6.3%) and 8% of a mixture of **5** and **6**. These products have the following properties.

Compound **4**: A yellow oil; the ^{1}H NMR spectral data is same as that reported:[5] FABMS (α-monothioglycelol as matrix): (m/e) 533 (100 %, [M + H]$^+$); HRMS (FAB, α-monothioglycelol as matrix): (m/e) calcd. for $C_{25}H_{33}O_{10}$ [M + H]$^+$: 533.2387, found 533.2400.

Mixture of **5** and **6**: Compounds **5** and **6** could not be separated. The ratio of **5** and **6** in the mixture was estimated to be 1:1 from the ratio of the aromatic ring protons and methylene protons of the side chain in the ^{1}H NMR spectrum (aromatic protons : methyl and methylene protons = 6.5:15). The intensities of parent ion peaks of **5** and **6** in the FAB MS were also 1:1. The total yield of **5** and **6** was 8%. A yellow oil; ^{1}H NMR: δ 8.24 - 7.36 (m, 6.5 H), 4.36 - 4.31 (m, 2H), 4.05 - 4.01 (m, 2H), 3.89 - 3.85 (m, 2H), 3.74 - 3.70 (m, 2H), 3.70 - 3.65 (m, 2H), 3.56 - 3.54 (m, 2H), 3.36 (s, 3H); FAB MS (α-monothioglycelol as matrix): (m/e) 405 (100 %, [M + H]$^+$ of **6**), 407 (50 %, [M + 2 + H]$^+$ of **6**), 371 (92 %, [M + H]$^+$ of **5**); FAB MS (α-monothioglycelol and sodium acetate as matrix): 427 (100 %, [M + Na]$^+$ of **6**), 429 (47 %, [M + 2 + H]$^+$ of **6**), 393 (98 %, [M + Na]$^+$ of **5**).

Reaction of 1,8-Dichloroanthraquinone and NaH. A mixture of 1,8-dichloroanthraquinone (0.50 g, 1.80 mmol) and NaH (60 % oil dispersion, 0.17 g, 4.25 mmol) in 30 mL of THF was stirred under reflux for 96 h. After the reaction mixture was treated in the usual manner, a residual yellow solid was chromatographed on silica gel ($CHCl_3$ as eluent) to recover 76% of 1,8-dichloroanthraquinone. No dechlorinated products were observed.

Reaction of (-)-1-Chloro-8-[1,4-dioxa-3-(*S*)-methyl-4-(tetrahydropyranyl)butyl]anthracene-9,10-dione (3) with NaH. A mixture of **3** (0.130 g, 0.32 mmol) and NaH (60 %, oil dispersion, 0.020 g, 0.50 mmol) in 10 mL of THF was stirred under reflux for 40 h. After the reaction mixture was treated manner described above, a residual yellow oil was chromatographed on silica gel ($CHCl_3$ as eluent) to give 72 mg of a mixture of **2** and **3**. The ratio between **2** and **3** in the mixture was estimated to be 1:3.5 from the ratio of the H_a proton of **2** and H_a proton of **3** in the ^{1}H NMR spectrum (12% and 43% yield, respectively).

Reaction of Sodium (*S*)-(-)-2-(Tetrahydropyranyloxy)-1-propoxide with (-)-1-Chloro-8-[1,4-dioxa-3-(*S*)-methyl-4-(tetrahydropyranyl)butyl]anthracene-9,10-dione (3). (*S*)-(-)-2-(Tetrahydropyranyloxy)-1-propanol (66 mg,

0.42 mmol) in 5 mL of dry THF was slowly added to a suspension of NaH (60% oil dispersion, 16 mg, 0.42 mmol) in 10 mL of dry THF at 0°C under an Argon atmosphere. The mixture was refluxed for 1 h and then stirred for 3 h at rt. Starting propanol derivative disappeared and 156 mg (0.39 mmol) of **3** was added and the solution was stirred under reflux for 40 h. The reaction mixture was treated in the same manner as described above. The crude product was chromatographed on a silica-gel column using $CHCl_3$ as the eluent to recover 78% of **3** and to give 9% of **1**. No dechlorinated product **2** was observed.

Acknowledgment

This work was supported by the Office of Naval Research.

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(*Received in USA* 3 *December* 1996; *revised* 29 *January* 1997; *accepted* 4 *February* 1997)