(0.65 mL, 7.2 mmol), freshly distilled from magnesium turnings, was dissolved in hexane (5 mL) under nitrogen, cooled to 0 °C, and treated with a 2.6 M solution of *n*-butyllithium (2.35 mL, 6.1 mmol) in hexanes. The resulting white suspension was stirred for 10 min and then concentrated to dryness under vacuum at 0 °C. Anhydrous hexamethylphosphoramide (12 mL) was then added, giving a 0.5 M solution of lithium 1-propanethiolate.

The methyl tetronate **2b** (0.3 g, 1.4 mmol) was dissolved in hexamethylphosphoramide (1.0 mL) under nitrogen and treated with a 0.5 M solution of lithium 1-propanethiolate (2.9 mL, 1.4 mmol) in hexamethylphosphoramide. After the mixture was stirred for 10 min, 1 M aqueous hydrochloric acid (25 mL) was added. The aqueous phase was extracted with diethyl ether (3 × 15 mL), and the combined extracts were washed with 1 M aqueous hydrochloric acid (10 mL) and brine (25 mL) and dried ($MgSO_4$). Evaporation yielded the crude tetronic acid **2c** (0.22 g, 80%). This was distilled on the Kugelrohr apparatus (oven temperature 240–250 °C/0.2 Torr). Trituration of the distilled oil with hexane gave a white solid: mp 105–108 °C; IR (KBr) ν 3100–2860, 1719, 1683 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.63 (s, 3 H), 1.7 (s, 3 H), 1.88 (br s, 3 H), 5.02 (d, J = 10 Hz, 1 H), 5.18 (d, J = 17 Hz, 1 H), 5.55 (br s, 1 H), 6.25 (dd, J = 10 and 17 Hz, 1 H), 10.4 (br s, 1 H) (The signal at δ 10.4 disappears upon shaking in D_2O.); MS, m/z 194 (4), 166 (7), 152 (17), 124 (24), 123 (18), 111 (52), 109 (41), 95 (100), 67 (34); MW calcd for $C_{11}H_{14}O_3$ 194.0943, found (HRMS) m/z 194.0935.

Acknowledgment. We acknowledge partial financial support of this investigation by the Natural Sciences and Engineering Research Council (NSERC) of Canada. One of us (M.J.D.) also acknowledges the award of an NSERC Postgraduate Scholarship, an Ontario Graduate Scholarship, and two University of Toronto Open Fellowships.

Preparation and Photoreaction of $6^A,6^B$-, $6^A,6^C$-, $6^A,6^D$-, and $6^A,6^E$-Bis(anthracene-9-carbonyl)-γ-cyclodextrins. A New Method for Regulation of Product Stereochemistry

Akihiko Ueno,* Fumio Moriwaki, Akiko Azuma, and Tetsuo Osa

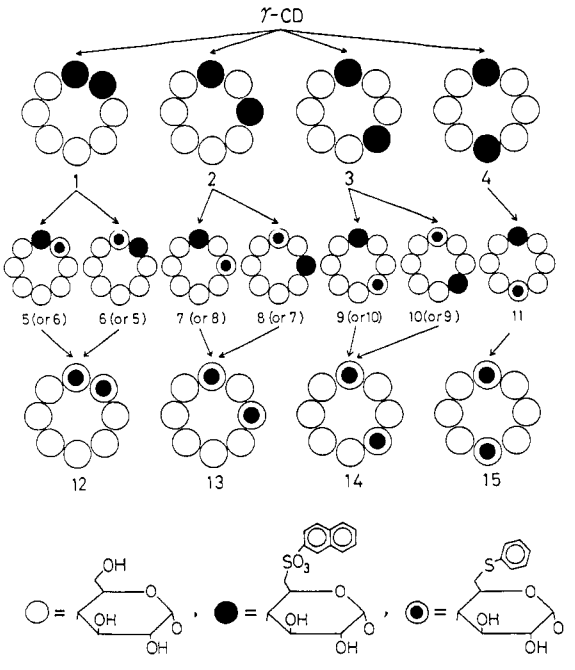
Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

Received June 23, 1988

Regioisomers of $6^A,6^X$-bis(anthracene-9-carbonyl)-γ-cyclodextrins were prepared by reactions of sodium 9-anthracenecarboxylate with regioisomers of $6^A,6^X$-bis(2-naphthylsulfonyl)-γ-cyclodextrins. The anthracene moieties of the bis(anthracene) regioisomers undergo photodimerization in a 10% ethylene glycol aqueous solution, affording a trans photodimer for $6^A,6^C$, $6^A,6^D$, and $6^A,6^E$ regioisomers and a cis photodimer for $6^A,6^B$ regioisomer. The photodimers of $6^A,6^D$ and $6^A,6^E$ regioisomers were stable, but those of $6^A,6^B$ and $6^A,6^C$ regioisomers were unstable and return toward the original anthracene monomers with half-lives of 12.5 and 275 min for $6^A,6^B$ and $6^A,6^C$ regioisomers, respectively. The dissociation of the photodimers is suggested to be due to the inherent property of cis photodimer for $6^A,6^B$ regioisomer and the strain-rich nature of trans photodimer for $6^A,6^C$ regioisomer.

Cyclodextrins are naturally occurring cyclic oligosaccharides and are known to form inclusion complexes with a variety of organic molecules in aqueous solution.[1] They are composed of six or more α-1,4-linked glucose units and called α-, β-, γ-cyclodextrins for six-, seven-, and eight-unit substances, respectively. The stoichiometry of complex formation is usually 1:1, but γ-cyclodextrin has been shown to form 1:2 host–guest complexes because of its larger cavity size.[2,3] This property of γ-cyclodextrin enables it to be used as a molecular flask, in which two species can meet and react as shown by facilitated formation of excimers,[3] charge transfer complexes,[4] and dimers.[5] In connection with this unique property of γ-cyclodextrin, host–guest complexation of some modified γ-cyclodextrins bearing one or two aromatic moieties has been studied.[6,7] In this study, we have attempted regulation of product stereochemistry, using regioisomers of disubstituted γ-cyclodextrins as templates, in which two

Scheme I



(1) Bender, M. L.; Komiyama, M. *Cyclodextrin Chemistry*; Springer-Verlag: New York, 1977.
(2) Ueno, A.; Takahashi, K.; Osa, T. *J. Chem. Soc., Chem. Commun.* **1980**, 921.
(3) Ueno, A.; Moriwaki, F.; Osa, T.; Hamada, F.; Murai, K. *Tetrahedron* **1987**, 43, 1571 and references therein.
(4) (a) Kobayashi, N.; Ueno, A.; Osa, T. *J. Chem. Soc., Chem. Commun.* **1981**, 340. (b) Kobayashi, N.; Saito, R.; Ueno, A.; Osa, T. *Makromol. Chem.* **1983**, *184*, 837.
(5) (a) Tamaki, T. *Chem. Lett.* **1984**, 53. (b) Tamaki, T.; Kokubu, T. *J. Inclusion Phenom.* **1984**, *2*, 815. (c) Tamaki, T.; Kokubu, T.; Ichimura, K. *Tetrahedron* **1987**, *43*, 1485.
(6) (a) Ueno, A.; Tomita, Y.; Osa, T. *J. Chem. Soc., Chem. Commun.* **1983**, 976. (b) Ueno, A.; Tomita, Y.; Osa, T. *Tetrahedron Lett.* **1983**, *24*, 5245. (c) Ueno, A.; Tomita, Y.; Osa, T. *Chem. Lett.* **1983**, 1635. (d) Ueno, A.; Moriwaki, F.; Tomita, Y.; Osa, T. *Chem. Lett.* **1985**, 493. (e) Ueno, A.; Moriwaki, F.; Hino, Y.; Osa, T. *J. Chem. Soc., Perkin Trans. 2* **1985**, 921. (f) Ueno, A.; Moriwaki, F.; Osa, T.; Hamada, F.; Murai, K. *J. Am. Chem. Soc.* **1988**, *110*, 4323.
(7) (a) Ueno, A.; Moriwaki, F.; Osa, T.; Hamada, F.; Murai, K. *Tetrahedron Lett.* **1985**, *26*, 3339. (b) Ueno, A.; Moriwaki, F.; Osa, T.; Hamada, F.; Murai, K. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 465.

0022-3263/89/1954-0295$01.50/0

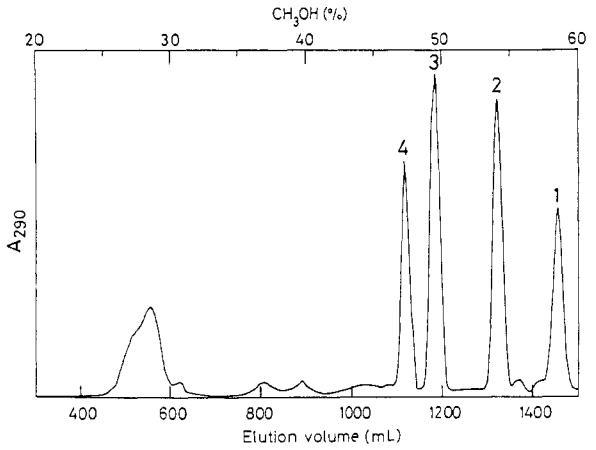
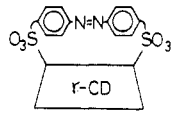


Figure 1. Separation of 1–4 by reversed-phase HPLC. A linear gradient elution of aqueous 10% CH_3OH–aqueous 60% CH_3OH was applied.

reactive substituents interact with each other differently among the regioisomers. In the case of disubstituted β-cyclodextrins, preparation and effective separation of regioisomers have been performed by Tabushi et al.[8-11] and Fujita et al.[12,13] This paper describes preparation, separation, and identification of regioisomers of disubstituted γ-cyclodextrins.

Preparation of $6^A,6^X$-Bis(2-naphthylsulfonyl)-γ-cyclodextrins (1–4). Regioisomers of $6^A,6^X$-bis(2-naphthylsulfonyl)-γ-cyclodextrins, which are precursors of $6^A,6^X$-bis(anthracene-9-carbonyl)-γ-cyclodextrins, were prepared by a reaction of γ-cyclodextrin and 2-naphthylsulfonyl chloride in pyridine. All regioisomers 1–4 were separable on HPLC through a reversed-phase column (Figure 1) and identified to be 6,6′-disulfonates by ^1H NMR, ^{13}C NMR, and FAB MS spectra. The assignments of 1–4 were carried out as shown in Scheme I. Compounds 1–4 were converted to corresponding 6,6′-bis(phenylsulfenyl)-γ-cyclodextrins (12–15) by treatment with thiophenol.[11] The products 12–15 were identified by ^1H NMR and FAB MS spectra. When the reaction process was monitored on HPLC, only one intermediate (11) was observed from 4, whereas two intermediates (5 and 6, 7 and 8, and 9 and 10) were observed from 1–3, respectively. This result suggests that 4 and 15 are $6^A,6^E$-disubstituted γ-cyclodextrins. When (*trans*-azobenzene-4,4′-disulfonyl)-γ-cyclodextrin (16) was used in place of 4, compounds 14



16

and 15 were obtained in a ratio of 6:94, which was estimated by HPLC analysis. This result suggests that *trans*-azobenzene-4,4′-disulfonyl dichloride (17) sulfonates 6^A and 6^E primary hydroxyls regioselectively, and may be related to the fact that 17 regioselectively sulfonates 6^A and 6^D primary hydroxyls of β-cyclodextrin.[14] Examination

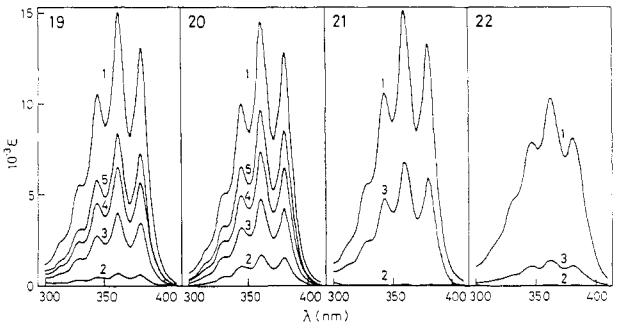
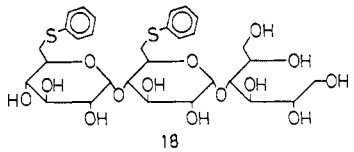


Figure 2. Absorption spectra of 19–22 before (1) and after (2) irradiation (λ > 300 nm). The spectra obtained by dissociation of the photodimers, which occurs thermally (19: 3, 30 min; 4, 60 min; 5, 90 min. 20: 3, 80 min; 4, 170 min; 5, 290 min) or photochemically (260-nm light irradiation) (3 for 21 and 22), are also shown.

of Corey–Pauling–Kolton (CPK) molecular models indicates that another possible isomer produced by the reaction of 17 and γ-cyclodextrin is $6^A,6^D$-disulfonyl-γ-cyclodextrin. Consequently, 14 was obtained as the minor product from 16. This result implies that the rest of the products, 12 and 13, should be $6^A,6^B$ (or $6^A,6^C$) and $6^A,6^C$ (or $6^A,6^B$) isomers.

Fujita et al. effectively used Taka-amylase-catalyzed hydrolysis to descriminate regioisomers of disubstituted β-cyclodextrins.[12] We also used this method to descriminate regioisomers 12 and 13. They reported that Taka-amylase-catalyzed hydrolysis of $6^A,6^B$-bis(phenylsulfenyl)-β-cyclodextrin followed by $NaBH_4$ reduction gave 18 as one of the major products. When the same treatment



18

was applied to 12, the product 18, which was identified by satisfactory ^1H NMR and FAB MS spectra, was obtained. This result demonstrates that 1 and 12 are $6^A,6^B$ isomers and consequently 2 and 13 are $6^A,6^C$ isomers. $6^A,6^B$-Bis(*tert*-butylsulfenyl)-β-cyclodextrin was reported to show isolated ^{13}C NMR chemical shifts for C-6, C-4, and C-1 of the A and B glucose units (C_6', C_4', and C_1', respectively).[11] Similar ^{13}C NMR chemical shift differences were observed in this study for C_6' of 2 and C_5' and C_6' of 1, supporting our determination of the modified positions.

Preparation of $6^A,6^X$-Bis(anthracene-9-carbonyl)-γ-cyclodextrins. Regioisomers of $6^A,6^X$-bis(anthracene-9-carbonyl)-γ-cyclodextrins were prepared by the reactions of sodium 9-anthracenecarboxylate and the corresponding regioisomers of $6^A,6^X$-bis(2-naphthylsulfonyl)-γ-cyclodextrins in dimethyl sulfoxide at 80 °C for 5 h. The products were purified by HPLC through a reversed-phase column and characterized by IR, UV, ^1H NMR, and FAB MS spectra and elemental analysis.

Results and Discussion

Irradiation of the regioisomers in a 10% ethylene glycol aqueous solution or methanol was performed with a 500-W xenon lamp using an appropriate cutoff filter for isolating UV light greater than 300 nm.[15] Figure 2 shows the

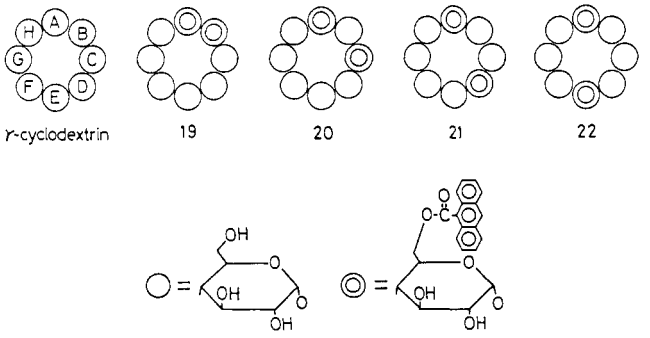
(8) Tabushi, I.; Kuroda, Y.; Yokota, K.; Yuan, L. C. *J. Am. Chem. Soc.* **1981**, *103*, 711.
(9) Tabushi, I.; Yuan, L. C. *J. Am. Chem. Soc.* **1981**, *103*, 3574.
(10) Tabushi, I.; Yamamura, K.; Nabeshima, T. *J. Am. Chem. Soc.* **1984**, *106*, 5267.
(11) Tabushi, I.; Nabeshima, T.; Fujita, K.; Matsunaga, A.; Imoto, T. *J. Org. Chem.* **1985**, *50*, 2638.
(12) Fujita, K.; Matsunaga, A.; Imoto, T. *Tetrahedron Lett.* **1984**, *25*, 5740.
(13) Fujita, K.; Matsunaga, A.; Ikeda, Y.; Imoto, T. *Tetrahedron Lett.* **1985**, *26*, 6439.
(14) Moriwaki, F.; Kaneko, H.; Ueno, A.; Osa, T.; Hamada, F.; Murai, K. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3619.
(15) Preliminary results obtained with a mixture of 21 and 22 were reported: Moriwaki, F.; Ueno, A.; Osa, T.; Hamada, F.; Murai, K. *Chem. Lett.* **1986**, 1865.

Table I. First-Order Dissociation Rate Constants and Half-Lives of Anthracene Dimers of 19 and 20 at 25 °C[a]

regioisomer	solvent[b]	10^5k,[c] s^{-1}	half-life, min
19	10% EG	92.3	12.5
19	MeOH	16.4	70.5
20	10% EG	4.20	275
20	MeOH	5.61	206

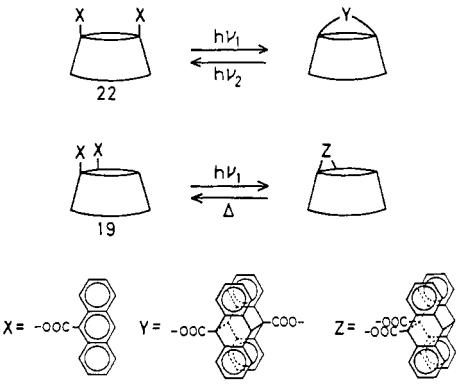
[a] The concentration of 19 and 20 was 2.5×10^{-5} M. [b] 10% EG = 10% ethylene glycol aqueous solution. [c] k = rate constant.

photoinduced spectral changes of all regioisomers together with the spectral variations occurring in the dark for **19** and **20** or by 260-nm light irradiation for **21** and **22** after photosteady states were reached. In all cases, the absorption around 365 nm decreased upon irradiation until its intensity became negligible for **21** and **22** or steady with the values smaller than 15% of the original absorptions for **19** and **20**. When the irradiated solutions were placed in the dark, it was found that the absorption spectra of **19** and **20** returned almost fully (90–100%) to the original absorbances, while those of **21** and **22** were unchanged. This spectral behavior indicates that **19** and **20** form unstable photodimers, which thermally dissociate into the starting anthracene moieties. The variations of the absorbance around 365 nm of **19** and **20** gave linear first-order plots, and the rate constants and half-lives are summarized in Table I. Dissociation occurs most rapidly in **19** in a 10% ethylene glycol aqueous solution, giving the half-life of 12.5 min at 25 °C. In methanol, the rate of dissociation was significantly depressed with 5.6-fold larger half-life. The photodimer of **20** also dissociates in a 10% ethylene glycol aqueous solution with the 22-fold larger half-life than that of **19**. The half-life of **20** in methanol is slightly smaller than that in a 10% ethylene glycol aqueous solution. Although **21** and **22** are stable in the dark, it has been shown that they can be partly (ca. 45% for **21**, 14% for **22**) converted to original monomer forms when irradiated with 260-nm light (Figure 2). The thermal or photochemical dissociation of the dimer forms of **19–22** might enable these substances to be used as molecular devices, in which host–guest complexation is controlled by light in an on–off fashion.



The regioisomers bearing anthracene monomers or a photodimer were analyzed on HPLC. The samples of the regioisomers containing an anthracene photodimer were prepared by irradiating methanol solutions of **19**, **20**, and **21** and a DMF solution of **22**. The use of DMF for **22** was due to a solubility problem. Since a linear gradient elution from a 20% acetonitrile aqueous solution toward pure acetonitrile (1%/min) was applied, the peak position can be shown by acetonitrile content. It is noted that the photodimer of **19** was so unstable that we could not observe any distinct peak for it. The HPLC data indicate that the regioisomers bearing anthracene monomers were eluted faster in the order of **22** > **21** > **20** > **19**, whereas those bearing an anthracene photodimer were eluted faster in the order of **20** > **21** > **22**. The HPLC charts of the regioisomers exhibit that **19** and **20** form minor side products by irradiation. These side products may have photooxidized anthracene moieties although the identification of the substances has not yet been performed.

Scheme II



The irradiated samples of **20**, **21**, and **22** were treated with an alkaline solution to hydrolyze the ester linkages. The photodimer of 9-anthracenecarboxylic acid thus obtained is the same as that formed by irradiation of 9-anthracenecarboxylic acid in methanol, showing an ^{1}H NMR chemical shift at 5.62 ppm, characteristic of the bridge-head protons of the trans photodimers. However, the same treatment of the irradiated sample of **19** gave no photodimer due to the complete dissociation of the photodimer. Examination of CPK models indicates that **19** cannot form the trans photodimer due to stereochemistry between the two 9-anthracenecarboxylate moieties; in other words, only **19** is capable of forming cis photodimer. Scheme II shows the photochemistry and stereochemistry of **19** and **22** as typical cases.

Usually irradiation of 9-substituted anthracenes gives only trans photodimer,[16] but in this study cis photodimer was formed by using **19** as a template although it is markedly unstable. The photodimer of **20** is also unstable in spite of its trans form. This may be due to the strain existing in the photodimer, which arises from connection of the photodimer to A and C positions of the γ-cyclodextrin framework.

Stereospecific photodimerization is well known to occur in crystals of some photoreactive monomers.[17] The present study has shown that similar stereochemical control in photodimerization can be attained in solution when aided by molecular templates such as γ-cyclodextrin. This new synthetic method might be widely applicable for regulation of product stereochemistry in reactions where two species form new covalent bonds.

Experimental Section

Measurements and Photodimerization. UV spectra were measured at 25 °C with a Shimadzu UV-250 spectrophotometer. NMR spectra were recorded on a JEOL JNM-GX 500 spectrometer. FAB MS spectra were obtained with a JEOL DX303 instrument. HPLC analysis was performed on a JASCO 800 series with use of TSK gel ODS-120A (4.6 × 250 mm) and YMC A-303 (ODS, 4.6 × 250 mm) columns. The column of YMC S-343 (I-15, ODS, 20 × 250 mm) was applied for preparative isolation of the products. Irradiation was performed with a 500-W xenon lamp (Ushio UXL-500D). A glass cutoff filter, which passes the light greater than 300 nm, was used. For special cases of 260-nm irradiation, a Shimadzu RF-500 instrument was used. Photodimerization proceeds in 1-cm quartz cells or in Pyrex vials. Rate

(16) *Organic Photophysics*; Birks, J. B., Ed.; Wiley: New York, 1975; p 496.
(17) Ramamurthy, V.; Venkatesan, K. *Chem. Rev.* **1987**, *87*, 433.

constants for dissociation of the photodimers of **19** and **20** were obtained by the first-order analysis for variations of the absorbance at 365 nm of the irradiated sample solutions (2.5×10^{-5} M, 3 mL) at 25 °C.

$6^A,6^B$-, $6^A,6^C$-, $6^A,6^D$-, and $6^A,6^E$-Bis(2-naphthylsulfonyl)-γ-cyclodextrins (1–4). A solution of γ-cyclodextrin (2.0 g, 1.5 mmol) and 2-naphthylsulfonyl chloride (2.0 g, 8.8 mmol) in dry pyridine (30 mL) was stirred for 4 h at room temperature. After the removal of pyridine, the resultant residue was dissolved in a small amount of water, and the pH of the solution was adjusted to become neutral with a NaOH solution. Small amounts of ethanol and water were added to the solution, and then the solvent mixture was removed under reduced pressure. This procedure was repeated several times until no pyridine odor was detected. After filtration, the water solution (8 mL) of the products was injected to a HPLC column (YMC S-343). While a gradient elution (10% MeOH–60% MeOH, 10 mL/min, 3 min/%) was applied, the UV absorption at 290 nm was monitored and fractions containing one of products were collected. After the removal of MeOH under reduced pressure, the resultant aqueous solutions were lyophilized to give **1** (59 mg, 2.3%), **2** (75 mg, 2.9%), **3** (78 mg, 3.0%), and **4** (61 mg, 2.4%). **1**: FAB MS, *m/e* 1699 ($[M + Na]^+$); ^1H NMR (Me_2SO-d_6) δ 3.05–3.75 (m), 4.18–4.69 (m, 10 H, O_6H, $C_6'H$), 4.69–4.94 (m, 8 H, C_1H), 5.65–5.88 (m, 16 H, O_2, O_3H), 7.67–7.87 (m, 6 H, aromatic), 8.01–8.19 (m, 6 H, aromatic), 8.52–8.60 (m, 2 H, aromatic); ^{13}C NMR (DMSO-d_6) δ 59.5–59.9 (C_6), 68.98 (C_5'), 69.13 (C_5'), 69.31 (C_6'), 69.61 (C_6'), 71.5–72.9 (C_2, C_2', C_3, C_3', C_5, C_5'), 80.2–81.0 (C_4, C_4'), 101.0–102.1 (C_1, C_1'), 122.3–134.8 (aromatic). **2**: FAB MS, *m/e* 1699 ($[M + Na]^+$); ^1H NMR (Me_2SO-d_6) δ 3.15–3.75 (m), 4.29–4.61 (m, 10 H, O_6H, $C_6'H$), 4.77–4.94 (m, 8 H, C_1H), 5.67–5.90 (m, 16 H, O_2, O_3H), 7.66–7.89 (m, 6 H, aromatic), 7.99–8.17 (m, 6 H, aromatic), 8.59 (s, 2 H, aromatic); ^{13}C NMR (Me_2SO-d_6) δ 59.3–59.9 (C_6), 69.23 (C_5'), 69.92 (C_6'), 70.10 (C_6'), 71.9–72.9 (C_2, C_2', C_3, C_3', C_5, C_5'), 80.0–81.2 (C_4, C_4'), 101.0–102.2 (C_1, C_1'), 122.3–134.7 (aromatic). **3**: FAB MS, *m/e* 1699 ($[M + Na]^+$); ^1H NMR (Me_2SO-d_6) δ 3.20–3.75 (m), 4.23–4.45 (m, 4 H, $C_6'H$), 4.48–4.70 (m, 6 H, O_6H), 4.76–4.96 (m, 8 H, C_1H), 5.70–5.92 (m, 16 H, O_2, O_3H), 7.65–7.80 (m, 6 H, aromatic), 7.99–8.15 (m, 6 H, aromatic), 8.50–8.55 (m, 2 H, aromatic); ^{13}C NMR (Me_2SO-d_6) δ 59.3–59.9 (C_6), 69.07 (C_5'), 69.91 (C_6'), 72.0–72.9 (C_2, C_2', C_3, C_3', C_5, C_5'), 80.2–81.1 (C_4, C_4'), 101.0–102.2 (C_1, C_1'), 122.2–134.7 (aromatic). **4**: FAB MS, *m/e* 1699 ($[M + Na]^+$); ^1H NMR (Me_2SO-d_6) δ 3.20–3.75 (m), 4.20–4.38 (m, 4 H, $C_6'H$), 4.42–4.69 (m, 6 H, O_6H), 4.76–4.95 (m, 8 H, C_1H), 5.70–5.95 (m, 16 H, O_2, O_3H), 7.66–7.78 (m, 6 H, aromatic), 7.99–8.15 (m, 6 H, aromatic), 8.53 (s, 2 H, aromatic); ^{13}C NMR (Me_2SO-d_6) δ 59.4–60.0 (C_6), 68.98 (C_5'), 69.80 (C_6'), 72.0–72.8 (C_2, C_2', C_3, C_3', C_5, C_5'), 80.2–81.1 (C_4, C_4'), 101.0–102.2 (C_1, C_1'), 122.2–134.7 (aromatic).

$6^A,6^B$-Bis(phenylsulfenyl)-γ-cyclodextrin (12). A solution of **1** (100 mg, 0.06 mmol) and sodium thiophenolate (160 mg, 1.2 mmol) in DMF (1.8 mL) was stirred at 80 °C for 14 h under nitrogen. To the reaction mixture was added a small amount of water, and the pH of the resultant solution (ca. 4 mL) was adjusted to become neutral with 1 N HCl, and then the solution was injected into a HPLC column (YMC S-343). While a gradient elution (10% MeOH–55% MeOH, 10 mL/min, 3 min/%) was applied, the UV absorption at 254 nm was monitored. After the removal of MeOH under reduced pressure from the collected fractions, which showed intense absorptions, the aqueous solution was lyophilized to give the desired product (31 mg, 35%) as white powder. This procedure was used for preparation of **13–15**. **12**: FAB MS, *m/e* 1481 ($[M + H]^+$); ^1H NMR (Me_2SO-d_6) δ 3.05–3.90 (m), 4.48–4.61 (m, 6 H, O_6H), 4.86–5.07 (m, 8 H, C_1H), 5.64–5.99 (m, 16 H, O_2, O_3H), 7.08–7.35 (m, 10 H, aromatic). **13**: FAB MS, *m/e* 1481 ($[M + H]^+$); ^1H NMR (Me_2SO-d_6) δ 3.03–3.85 (m), 4.50–4.59 (m, 6 H, O_6H), 4.86–5.01 (m, 8 H, C_1H), 5.70–5.98 (m, 16 H, O_2, O_3H), 7.04–7.33 (m, 10 H, aromatic). **14**: FAB MS, *m/e* 1481 ($[M + H]^+$); ^1H NMR (Me_2SO-d_6) δ 3.05–3.87 (m), 4.47–4.60 (m, 6 H, O_6H), 4.86–5.00 (m, 8 H, C_1H), 5.68–5.96 (m, 16 H, O_2, O_3H), 7.08–7.35 (m, 10 H, aromatic). **15**: FAB MS, *m/e* 1481 ($[M + H]^+$); ^1H NMR (Me_2SO-d_6) δ 3.03–3.88 (m), 4.47–4.62 (m, 6 H, O_6H), 4.86–5.01 (m, 8 H, C_1H), 5.68–5.97 (m, 16 H, O_2, O_3H), 7.10–7.30 (m, 10 H, aromatic).

Taka-Amylase Hydrolysis of 12. The compound **12** (25 mg, 0.017 mmol) was hydrolized by Taka-amylase (Sigma X-A, 25 mg) according to the method reported previously.[11] After the usual workup, the reaction mixture was injected into a HPLC column (YMC S-343). While a gradient elution (10% EtOH–50% EtOH, 10 mL/min, 2 min/%) was applied at 35 °C, the UV absorption at 254 nm was monitored. As one of the major products, **18** was obtained after removing EtOH under reduced pressure, followed by lyophilization (1.3 mg, 11%). **18**: FAB MS, *m/e* 691 ($[M + H]^+$), 509, 255 (fragments of **18**); ^1H NMR (Me_2SO-d_6) δ 2.92–3.82 (m), 4.10–4.16 (m, 1 H), 4.46–4.54 (m, 4 H, OH), 4.55 (d, J = 5.0 Hz, 1 H, OH), 4.92 (d, J = 3.8 Hz, 1 H, $C_1'H$ or $C_1''H$), 5.03 (d, J = 5.0 Hz, 1 H, OH), 5.11 (d, J = 3.6 Hz, 1 H, $C_1'H$ or $C_1''H$), 5.23 (d, J = 5.3 Hz, 1 H, OH), 5.59 (d, J = 6.3 Hz, 1 H, OH), 5.64 (d, J = 6.3 Hz, 1 H, OH), 5.66 (d, J = 3.3 Hz, 1 H, OH), 7.07–7.36 (m, 10 H, aromatic).

$6^A,6^B$-Bis(anthracene-9-carbonyl)-γ-cyclodextrin (19). A solution of sodium 9-anthracenecarboxylate (87 mg, 0.36 mmol) and **1** (150 mg, 0.089 mmol) in DMSO (1 mL) was stirred at 80 °C for 5 h. The reaction mixture was poured into acetone (50 mL), and the precipitates that formed were collected, washed with acetone and ether, and dried under reduced pressure in the dark. The solid was dissolved in a mixture of DMF (2 mL) and water (1 mL) and injected into a HPLC column (YMC S-343) after passing through a filter (chromatodisk 13L). While a gradient elution (50% MeOH–80% MeOH, 10 mL/min, 2 min/%) was applied after initial elution with 20% MeOH (ca. 50 mL), the UV absorption at 365 nm was monitored. The fractions collected were concentrated under reduced pressure to give crystals of **19** (75 mg, 46%). This procedure was used for preparation of **20–22**. **19**: FAB MS, *m/e* 1705 ($[M + H]^+$); IR (KBr) 1720 cm^{-1}; ^1H NMR (Me_2SO-d_6) 3.18–3.85 (m), 4.02–4.29 (m, 2 H, $C_5'H$), 4.48–4.65 (m, 7 H, O_6H, $C_6'H$), 4.73–5.18 (m, 11 H, C_1H, $C_6'H$), 5.63–5.97 (m, 16 H, O_2, O_3H), 7.23–7.63 (m, 8 H, aromatic), 7.94–8.18 (m, 8 H, aromatic), 8.74 (s, 1 H, aromatic), 8.79 (s, 1 H, aromatic). Anal. Calcd for $C_{78}H_{96}O_{42}\cdot 7H_2O$: C, 51.14; H, 6.05. Found: C, 51.14; H, 5.45. **20**: FAB MS, *m/e* 1705 ($[M + H]^+$); IR (KBr) 1720 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.19–3.81 (m), 3.98–4.05 (br, 2 H, $C_5'H$), 4.49–4.69 (m, 8 H, O_6H, $C_6'H$), 4.81–5.04 (m, 10 H, C_1H, C'_6H), 5.71–5.98 (m, 16 H, O_2,O_3H), 7.55–7.64 (m, 8 H, aromatic), 8.04–8.21 (m, 8 H, aromatic), 8.74 (s, 1 H, aromatic), 8.81 (s, 1 H, aromatic). Anal. Calcd for $C_{78}H_{96}O_{42}\cdot 5H_2O$: C, 52.17; H, 5.95. Found: C, 52.25; H, 6.08. **21**: FAB MS, *m/e* 1705 ($[M + H]^+$); IR (KBr) 1720 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.20–3.80 (m), 3.97–4.07 (m, 2 H, $C_5'H$), 4.42–4.70 (m, 8 H, O_6H, $C_6'H$), 4.84–5.03 (m, 10 H, C_1H, $C_6'H$), 5.67–5.93 (m, 16 H, O_2,O_3H), 7.56–7.65 (m, 8 H, aromatic), 8.05–8.22 (m, 8 H, aromatic), 8.75 (s, 1 H, aromatic), 8.81 (s, 1 H, aromatic). Anal. Calcd for $C_{78}H_{96}O_{42}\cdot 8H_2O$: C, 50.64; H, 6.10. Found: C, 50.46; H, 5.74. **22**: FAB MS, *m/e* 1705 ($[M + H]^+$); IR (KBr) 1720 cm^{-1}; ^1H NMR (Me_2SO) δ 3.15–3.85 (m), 4.00–4.05 (m, 2 H, $C_5'H$), 4.38–4.62 (m, 8 H, O_6H, $C_6'H$), 4.83–5.04 (m, 10 H, C_1H, $C_6'H$), 5.67–5.91 (m, 16 H, O_2, O_3H), 7.49–7.58 (m, 8 H, aromatic), 7.98–8.05 (m, 8 H, aromatic), 8.56 (s, 2 H, aromatic). Anal. Calcd for $C_{78}H_{96}O_{42}\cdot 7H_2O$: C, 51.14; H, 6.05. Found: C, 50.90; H, 6.04.

HPLC Analysis of Intermediates 5–11. A solution of **1** (2 mg, 0.0012 mmol) and sodium thiophenolate (0.8 mg, 0.006 mmol) in DMF was stirred under nitrogen at room temperature for 15 min and then at 60 °C for 30 min. To the solution was added sodium thiophenolate (1.6 mg, 0.012 mmol), and the stirring was continued for another 30 min at 60 °C. The reaction mixtures obtained at various reaction times were respectively injected into a HPLC column (YMC A-303). While a gradient elution (15% MeCN–45% MeCN, 1 mL/min, 1 min/%) was applied at 35 °C, the UV absorption at 254 nm was monitored. Two peaks corresponding to the intermediates **5** and **6** (36.6 and 36.8% MeCN, respectively) were observed between the peaks of the starting compound **1** and the final product **12** (40.7 and 32.6% MeCN, respectively). The same procedure was used for analyses of **7–11**; the HPLC peak positions were 39.1 (**2**), 36.3 (**3**), 35.2 (**4**), 34.4, 35.0 (**7**, **8**), 31.9, 32.9 (**9**, **10**), 31.8 (**11**), 30.6 (**13**), 29.3 (**14**), and 28.5% (**15**) CH_3CN.

HPLC Analysis of the Products Obtained by a Reaction of 16 and Sodium Thiophenolate. A mixture of **16** (1 mg, 6.2×10^{-7} mol) and sodium thiophenolate (1.6 mg, 1.2×10^{-5} mol) in DMF (0.5 mL) was stirred at 80 °C for 4 h under nitrogen. The reaction mixture was injected into a HPLC column (YMC A-303). The same gradient elution as described above in the analyses of

5-11 was applied. Two peaks corresponding to **14** and **15** were observed at the respective ratio of 6:94.

HPLC Analysis of Irradiated Samples of 19-22. The solution of **19** in MeOH (5.5×10^{-4} M) before and after irradiation were analyzed on HPLC with a reversed-phase column (TSK gel ODS-120A). While a gradient elution (20% CH_3CN–50% CH_3CN, 1 mL/min, 1 min/%) was applied at 35 °C, the UV absorption at 221 nm was monitored. The same procedure was used for analyses of **20-22** except for the use of DMF in place of MeOH for **22** as the solvent of the sample solution due to solubility problem. The HPLC peak positions of these substances before irradiation were 46.0, 44.3, 41.7, and 36.9% CH_3CN for **19**, **20**, **21**, and **22**, respectively. The elution order of these substances became opposite after irradiation as shown by the peaks positioned at 24.8, 30.8, and 31.7% CH_3CN for **20**, **21**, and **22**, respectively. No peak was observed for the photodimer of **19** due to its short life-time.

Hydrolysis of Irradiated Samples of 19-22. The solution of **22** in MeOH (5 mL, 1.0×10^{-4} M) was irradiated for 1 h, and the solvent was removed under reduced pressure. To the solid residue was added a 4 N NaOH solution, and the solution was stirred overnight. The reaction mixture was neutralized with a HCl solution (4 N) and injected into a HPLC column (ODS-120A). A solution composed of 45% CH_3CN and 55% buffer (0.2 M $Et_3N{\cdot}H_3PO_4$, pH 3) was used as eluent. The same procedure was used for hydrolysis of **19-21**.

Photodimerization of 9-Anthracenecarboxylic Acid. A mixture of 9-anthracenecarboxylic acid (40 mg) and MeOH (20 mL) was irradiated for 6 h under nitrogen, and then the solvent was removed under reduced pressure. Silica gel column chromatography with *n*-hexane/ether/AcOH (75:25:1 and 50:50:1) gave the photodimer (30%): NMR (DMSO-d_6) δ 5.62 (s, 2 H), 6.75-6.90 (m, 16 H).

Acknowledgment. Support of this work by Grants-in-Aid 61470152, 61550585, and 62790303 from the Ministry of Education, Science and Culture of Japan is greatfully acknowledged.

Intramolecular Cyclopropanation Reaction of Furanyl Diazo Ketones

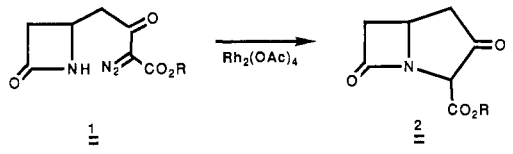
Albert Padwa,* Thomas J. Wisnieff, and Edward J. Walsh†

Department of Chemistry, Emory University, Atlanta, Georgia 30322

Received August 16, 1988

α-Diazo ketones derived from furanyl- and benzofuranylpropionic acids were prepared, and their rhodium(II) acetate catalyzed behavior was studied. The results are consistent with a mechanism in which the key step involves addition of a keto carbenoid intermediate on to the furanyl π-bond followed by an electrocyclic ring-opening reaction. In the case of the benzo-substituted furanyl system, the suspected bicyclic intermediate was isolated in high yield and its chemistry was subsequently investigated. The bicyclic ketone derived from 1-diazo-4-(2-benzofuryl)-2-butanone undergoes a novel thermal rearrangement to a benzopyranone derivative. This unexpected transformation can be rationalized in terms of a [4 + 2]-cycloreversion reaction to give an ortho-quinoidal intermediate, which undergoes a subsequent electrocyclic ring closure followed by a 1,3-hydrogen shift. Furans with side chains of various lengths containing a diazomethyl keto group were also studied. The cyclization chemistry of the closely related diazothienylalkanone system was investigated and found to give products derived from an analogous intramolecular cyclopropanation reaction.

α-Diazo carbonyl compounds have been widely studied under thermal, photochemical, and transition metal catalyzed conditions.[1,2] Intramolecular cyclization of α-carbonyl carbenes and carbenoids derived from α-diazo ketones has found widespread application for the preparation of a variety of theoretically and biologically interesting compounds.[3-11] Probably one of the more significant insertion reactions of recent years is outlined below



1 2

and represents the key step in the Merck synthesis of carbapenams.[12,13] Since rhodium-catalyzed decomposition of diazo ketones involves a rhodium carbenoid intermediate rather than a free carbene,[14,15] the above type of ring closure is probably better regarded as nucleophilic attack by the lactam NH on the rhodium carbenoid, rather than an insertion into the NH bond.

Transition metal mediated intramolecular additions to π-bonds have also been extensively utilized in carbocyclic synthesis. A general review of intramolecular diazo carbonyl reactions appeared in 1979,[2] and since then, many further publications on transition metal catalyzed reactions

†Department of Chemistry, Allegheny College, Meadville, PA.

(1) Moody, C. J. *Organic Reaction Mechanisms*; Wiley: London, 1983; Chapter 6.
(2) For a recent comprehensive review, see: Burke, S. D.; Grieco, P. A. *Org. React. (N.Y.)* **1979**, *26*, 361.
(3) Doering, W. V. E.; Ferrier, B. M.; Fossel, E. T.; Hartenstein, J. H.; Jones, M., Jr.; Klumpp, G.; Rubin, R. M.; Saunder, M. *Tetrahedron* **1967**, *23*, 3943.
(4) Vogel, E.; Reel, H. *J. Am. Chem. Soc.* **1972**, *94*, 4388.
(5) Doering, W. V. E.; Pomerantz, M. *Tetrahedron Lett.* **1964**, 961.
(6) Irngartinger, H.; Goldman, A.; Schappert, R.; Garner, P.; Dowd, P. *J. Chem. Soc., Chem. Commun.* **1981**, 455.
(7) Trost, B. M.; Vladuchick, W. C. *J. Org. Chem.* **1979**, *44*, 148.
(8) Stork, G.; Ficini, J. *J. Am. Chem. Soc.* **1961**, *83*, 4678.
(9) Grieco, P. A. *J. Am. Chem. Soc.* **1969**, *91*, 5660.
(10) Corey, E. J.; Achiwa, K.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1969**, *91*, 4318.
(11) White, J. D.; Torii, S.; Nogami, J. *Tetrahedron Lett.* **1974**, 2879.
(12) Ratcliffe, R. W.; Salzmann, T. N.; Christensen, B. G. *Tetrahedron Lett.* **1980**, *21*, 31.
(13) Saltzmann, T. N.; Ratcliff, R. W.; Christensen, B. G.; Bouffard, F. A. *J. Am. Chem. Soc.* **1980**, *102*, 6161.
(14) Doyle, M. P. *Acc. Chem. Res.* **1986**, *19*, 348. Doyle, M. P.; Dorow, R. L.; Buhro, W. E.; Griffin, J. H.; Tamblyn, W. H.; Trudell, M. L. *Organometallics* **1984**, *3*, 44. Doyle, M. P.; Van Leusen, D.; Tamblyn, W. H. *Synthesis* **1981**, 787; *Chem. rev.* **1986**, *86*, 919.
(15) Paulissen, R.; Reimlinger, H.; Hayez, E.; Hubert, A. J.; Teyssie, P. *Tetrahedron Lett.* **1973**, 2233. Hubert, A. J.; Noels, A. F.; Anciaux, A. J.; Teyssie, P. *Synthesis* **1976**, 600; *J. Chem. Soc., Chem. Commun.* **1980**, 765. Anciaux, A. J.; Hubert, A. F.; Noels, N.; Petiniot, N.; Teyssie, P. *J. Org. Chem.* **1980**, *45*, 695.

0022-3263/89/1954-0299$01.50/0