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# COMPLEXES OF CYCLOMALTOHEPTAOSE WITH AROMATIC DIAZO COMPOUNDS: FORMATION AND REACTIONS

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ABSTRACT

Pyrolysis of the relatively stable, solid complexes of cyclomaltoheptaose (β-cyclodextrin) with phenyldiazomethane, 1-diazo-1-phenylethane, and diazo-(diphenyl)methane results in degradation of the labile guests. The host matrix exerts "reaction-vessel" and "shape-selectivity" effects upon the reaction pathways of the guests and derivatives. The carbene insertion reaction with the β-cyclodextrin hydroxyl groups is regioselective.

## INTRODUCTION

Cyclomalto-oligosaccharides (cyclodextrins, CDs) can control, modify, and enhance various reactions[1]. Their ability to bind small molecules, coupled with the possibility of derivatization of their hydroxyl groups, makes them ideal models for enzymes. Many CD derivatives have been synthesized[2] and some show remarkable enzyme-like catalytic activity[3]. Although a main interest in CDs concerns their influence on bio-organic reactions, recent studies have explored their effects on other chemistry both in solution and the solid-state. Since CDs form channel and cage structures in the solid-state[1], they often provide greater control of the reactions of trapped guest molecules than in the liquid phase. Unlike reactions in solution, reactions in the solid-state must be initiated because the inclusion complex must be made prior to the reaction step. If the guests are too reactive, then they will react during the formation of the inclusion complexes (see below). Two initiation techniques are photolysis and pyrolysis. There have been several studies of the photochemistry of CD-bound guests[4], but the corresponding pyrolysis reactions have received relatively little attention.

Our interest concerns the reactions of thermally generated reactive intermediates inside the cavity of the CD in the solid-state. The CD may not only control the reaction pathways of the intermediate, but also may react regio- and/or stereoselectively with the intermediate. There have been few studies of highly reactive intermediates generated within the cavities of CDs. Radical pairs have been

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generated photochemically[4,5] and their coupling and disproportionation reactions are influenced greatly by the CD. Radical pairs also can be generated thermally, for example, through the decomposition of azobisisobutyronitrile[5]. Carbenes are often more reactive than radical pairs, and, in the presence of cyclomaltoheptaose (βCD), dichlorocarbene selectively attacked the *p*-position of phenoxide to give *p*-hydroxybenzaldehyde (Reimer–Tiemann reaction)[6].

βCD exerts considerable influence on the reactions of phenylmethyldiazirine under thermal and photochemical conditions[7], and the main product was *trans*-1-methyl-1,2-diphenylcyclopropane. This result contrasts with those of studies of reactions in solution where the azine product preponderated[8]. Also, the selectivity for the *trans* isomer was ten-fold higher from the βCD complex than for reactions in solution. These results were interpreted in terms of "reaction vessel" and "shape-selectivity" effects. In the former effect, βCD retards certain bimolecular reactions relative to the intramolecular H-shift which produces styrene, whereas, in the latter effect, formation of the *trans* isomer is favored because the phenyl groups are aligned axially in the cavity of βCD.

The use of a diazirine as a precursor for a carbene has advantages and disadvantages over the use of a diazo compound. Unlike diazo compounds, diazirines are relatively inert towards acids, so that they do not decompose when stirred with an aqueous solution of βCD, the method for the formation of inclusion complexes. One disadvantage is the difficulty in synthesis. Thus, structurally related diazirines may require different syntheses. Moreover, diazirines decompose thermally[8] via isomerization to the diazo compound which then loses $N_2$. Thus, two intermediates are formed during their decomposition, thereby making the chemistry complicated.

We now report on the reactions of the complexes of βCD with the structurally related diazo compounds, diazo(phenyl)methane (**1a**), 1-diazo-1-phenylethane (**1b**), and diazo(diphenyl)methane (**1c**).

## EXPERIMENTAL

*General methods.* — N.m.r. spectra were recorded with Varian FT-80A and QE-300 spectrometers. U.v. and i.r. spectra were obtained using Beckman DU-70 and Perkin–Elmer 1320 spectrophotometers, respectively. G.l.c. was performed on a Hewlett–Packard 5790A instrument, using a 23-m-capillary column of 5% phenylmethylsilicone or a 30-m-capillary column of OV-1 and a flame-ionization detector. H.p.l.c. was performed with a Waters 244 liquid chromatograph equipped with a u.v. detector (254 nm) and a Whatman Magnum 20 column (22 × 500 mm) packed with Partisil-10 ODS. Combustion analyses were performed by Desert Analytics (Tuscon, Arizona). β-Cyclodextrin was provided by Amaizo.

*Diazo compounds.* — *Method A.* Tosylhydrazones of benzaldehyde and acetophenone were prepared by condensation of the carbonyl compound with tosylhydrazine[9]. The diazo compounds were generated by vacuum pyrolysis of the

tosylhydrazone sodium salts, and were condensed in an ice/EtOH-cooled flask*. The purity of the samples was determined by n.m.r. spectroscopy. Diazo compounds taken directly from the preparation were >90% pure.

*Method B.* Hydrazones of benzaldehyde, acetophenone, and benzophenone were made by condensation of the carbonyl compound with aqueous 85% hydrazine hydrate, using CaO as a dehydrating agent[10]. The diazo compounds were generated[11] by oxidation of the hydrazones using yellow HgO [freshly prepared from $Hg(NO_3)_2$ and KOH] and a catalytic amount of KOH.

*Inclusion complexes. — Diazo(phenyl)methane–β-cyclodextrin* (**2a**). *Method A.* A solution of diazo(phenyl)methane (850 mg, 7.2 mmol) in $Et_2O$ (30 mL) was placed above a solution of βCD (12.0 g, 10.6 mmol) in $H_2O$ (200 mL) at 10°. The solutions were stirred rapidly with cooling (ice-bath), and a stream of $N_2$ was directed over the $Et_2O$ layer. After 6 h, the $Et_2O$ layer had disappeared, and the pink solid was collected, washed with water, and dried for 1 day *in vacuo* to afford **2a** (5.1 g, 54% based on diazo compound). N.m.r. spectroscopy indicated a guests/βCD ratio of 0.9. The guest distribution (% based on integration of signals in the region for aromatic protons) was diazo(phenyl)methane (59), *E,Z*-azine (21), *E,E*-azine (1); *E,Z/E,E* ratio, 21. A portion (2.34 g) of **2a** was digested in boiling HOAc (25 mL) for 10 min. The mixture was diluted with $H_2O$ (250 mL) and extracted with $Et_2O$ (3 × 50 mL), and the combined extracts were washed with saturated aqueous $NaHCO_3$ and dried ($Na_2SO_4$). Capillary g.l.c. of the solution gave the results shown in Table I, entry 1. Removal of the solvent *in vacuo* left 270 mg of material (97% yield of guests and derivatives).

*Method B.* A solution of benzaldehyde hydrazone (3.7 g, 31 mmol) in $Et_2O$ (5 mL) was added to a slurry of HgO (11.9 g, 55 mmol) in $Et_2O$ (30 mL) containing saturated ethanolic KOH (1 mL). The mixture was stirred vigorously for 1 h with cooling (water-bath). The i.r. spectrum of an aliquot of the mixture showed that some hydrazone remained. More HgO (3.0 g, 14 mmol) was added, and stirring was continued for 30 min. The mixture was filtered into a solution of βCD (27.0 g, 23.8 mmol) in water (400 mL). The solutions were stirred and processed as described above to give **2a** (18.6 g, 62% based on βCD). N.m.r. spectroscopy indicated a guests/βCD ratio of 0.5. The guest distribution (%) was diazo(phenyl)methane (65), *E,Z*-azine (3), *E,E*-azine (4); *E,Z/E,E* ratio, 0.66. A portion (3.01 g) of the complex was digested with boiling HOAc (25 mL) for 10 min. Work-up as above gave 136 mg of material (82% yield of guests and derivatives). The product distribution is reported in Table I, entry 2.

*1-Diazo-1-phenylethane–β-cyclodextrin* (**2b**). *— Method A.* A solution of 1-diazo-1-phenylethane (560 mg, 4.2 mmol) in $Et_2O$ (50 mL) was placed above a solution of βCD (7.9 g, 7.0 mmol) in $H_2O$ (150 mL). The mixture was processed as for **2a** to give **2b** as a creamy purple solid (3.2 g, 93% yield based on diazo compound). N.m.r. spectroscopy of the solid showed a guests/βCD ratio of 1.3:1. The

*Diazo compounds are toxic and potentially explosive, and appropriate safeguards should be used.

guest distribution (% based on integration of signals in the region for aromatic protons) was 1-diazo-1-phenylethane (61), acetophenone (1), *E,E*-azine (2), *E,Z*-azine (23), *Z,Z*-azine (14); (*E,Z* + *Z,Z*)/*E,E* ratio, 22. A portion (1.7 g) of the complex was digested in boiling HOAc (25 mL) for 10 min. Work-up as above gave 231 mg of material (74% yield of guests and derivatives). The distribution of products determined by g.l.c. is given in Table I, entry 4.

*Method B.* Acetophenone hydrazone (3.6 g, 27 mmol) in $Et_2O$ (10 mL) was added to a slurry of HgO (11.8 g, 55 mmol) in $Et_2O$ (30 mL) containing saturated ethanolic KOH (1 mL). $Na_2SO_4$ (4 g) was then added, and the solution was stirred vigorously for 15 min with cooling (water-bath). The i.r. spectrum of an aliquot of the mixture showed the reaction to be complete. The mixture was filtered onto a solution of βCD (27.0 g, 23.8 mmol) in water (400 mL), and the mixture was processed as for **2a** to give **2b** (22.5 g, 69% based on hydrazone). N.m.r. spectroscopy indicated a guests/βCD ratio of 0.8. The guest distribution (%) was 1-diazo-1-phenylethane (57), acetophenone (4), *E,E*-azine (5), *E,Z*-azine (27), *Z,Z*-azine (7); (*E,Z* + *Z,Z*)/*E,E* ratio, 6.8. A portion (3.0 g) of the complex was digested with boiling HOAc (40 mL) for 10 min. Work-up as above and analysis by g.l.c. gave the product distribution reported in Table I, entry 6.

*Diazo(diphenyl)methane–β-cyclodextrin* (**2c**). — *Method B.* Benzophenone hydrazone (1.3 g, 6.6 mmol), yellow HgO (3.5 g, 14 mmol), and $Na_2SO_4$ (1.7 g, 12 mmol) were stirred rapidly with $Et_2O$ (20 mL) containing saturated ethanolic KOH (0.5 mL) in a flask wrapped with a wet paper towel. After 3 h, the solution was filtered onto a saturated aqueous solution of βCD (11.4 g, 10.0 mmol; 280 mL of $H_2O$), and the mixture was processed as for **2a** to give **2c** (8.1 g, 96% based on hydrazone) as a purple solid. N.m.r. spectroscopy indicated a guests/βCD ratio of 1.0. The guest distribution (%) was diazo(diphenyl)methane (92), benzophenone (3), azine (<5). A portion (2.3 g) of the complex was digested in HOAc (20 mL). Work-up as above afforded 320 mg of material (80% yield of guest and derivatives). Analysis by g.l.c. gave the product distribution shown in Table I, entry 7.

*Pyrolysis of the βCD complexes.* — The complex was stirred at 180–200° until the color of the diazo compound disappeared (~5 min). The residue was cooled, a solution in $H_2O$ was extracted thrice with $Et_2O$, and the combined extracts were dried and concentrated *in vacuo*. The residue was analyzed by g.l.c. and n.m.r. spectroscopy. The aqueous layer was concentrated *in vacuo*, and the residue was subjected to flash reverse-phase chromatography (Baker, C-18) using a gradient elution (0→40% $CH_3CN$–$H_2O$). The fractions containing βCD derivatives (t.l.c.) were combined and concentrated *in vacuo*. The mono-derivatives in these fractions were separated by h.p.l.c. using a gradient elution (20→30% $CH_3CN$–$H_2O$) at 18 mL/min.

*Diazo(phenyl)methane–β-cyclodextrin.* — The complex (1.75 g, 1.41 mmol; guest/host ratio, 0.9:1; 78 mol% diazo guest; generated via method A) was pyrolyzed at 185–186° for 5 min. The $Et_2O$-soluble products (137 mg, 84%) were analyzed by g.l.c., and the product distribution (%) was *cis*-stilbene (19), *trans*-

stilbene (7), deoxybenzoin (21), and benzaldehyde azine (53). The *O*-benzyl-βCDs (340 mg, 0.28 mmol, 29%) were isolated by flash reverse-phase chromatography, $R_F$ 0.58 (5:4:3 *n*-BuOH–EtOH–$H_2O$). The mixture gave two fractions in h.p.l.c., 76% (*T* 28 min) and 24% (34). Fraction 1 was identified as a mixture of 2- and 3-*O*-benzyl-βCD. N.m.r. data: $^1H$ [$(CD_3)_2SO$, $D_2O$], δ 7.43–7.23 (m, 5 H, Ph), 4.77 (d, 1 H, *J* 12.3 Hz, PhC$H_2$), 4.68 (d, 1 H, *J* 12.3 Hz, PhC$H_2$); $^{13}C$ [$(CD_3)_2SO$], δ 138.1, 138.0, 128.9, 128.5, 128.2, 128.1, 127.9, 127.7, 102.1, 101.9, 101.2, 100.4, 82.4, 81.8, 81.7, 81.6, 81.4, 80.2, 79.5, 78.2, 73.8, 73.7, 73.5, 73.2, 72.9, 72.7, 72.5, 72.2, 71.9, 60.0.

*Anal.* Calc. for $C_{49}H_{76}O_{35}\cdot 2\ H_2O$: C, 46.67; H, 6.39. Found: C, 46.63; H, 6.21.

Fraction 2 was 6-*O*-benzyl-βCD. N.m.r. data: $^1H$, δ 7.48–7.23 (m, 5 H, Ph), 4.53 (d, 1 H, *J* 11.8 Hz, PhC$H_2$), 4.44 (d, 1 H, *J* 11.8 Hz, PhC$H_2$): $^{13}C$ δ 138.8, 130.0, 127.6, 127.5, 102.6, 102.1, 82.3, 81.7, 73.9, 73.2, 72.6, 72.2, 70.6, 69.0, 60.1.

*Anal.* Calc. for $C_{49}H_{76}O_{35}\cdot 3\ H_2O$: C, 46.01; H, 6.46. Found: C, 45.77; H, 6.35.

*1-Diazo-1-phenylethane–β-cyclodextrin.* — The complex (1.51 g, 1.1 mmol, guest/host ratio, 1.3:1; 75 mol% diazo guest; generated via method A) was decomposed at 183–190° for 5 min. The $Et_2O$-soluble products (108 mg, 0.57 mmol, 51%) were analyzed by g.l.c., and the product consisted (%) of acetophenone (21), 1-phenylethanol (<1), *cis*-1-methyl-1,2-diphenylcyclopropane (1), *trans*-1-methyl-1,2-diphenylcyclopropane (27), *trans*-dimethylstilbene (<1), and acetophenone azine (50). The *O*-1-phenethyl-βCDs (410 mg, 29%) were isolated by flash reverse-phase chromatography, $R_F$ 0.59 (5:4:3 *n*-BuOH–EtOH–$H_2O$). This material was separated into four fractions by h.p.l.c.: 23% (*T* 26 min), 34% (34), 25% (37), and 18% (41). Fraction 1 was identified as 2-*O*-(1-phenethyl)-βCD. N.m.r. data: $^1H$ [$(CD_3)_2SO$, $D_2O$], δ 7.59–7.32 (m, 5 H, Ph), 5.55 (q, 1 H, *J* 6.5 Hz, $CH_3CH$), 1.46 (d, 3 H, *J* 6.5 Hz, $CH_3CH$); $^{13}C$ [$(CD_3)_2SO$], δ 141.2, 128.7, 128.4, 102.7, 102.2, 101.9, 101.1, 82.0, 81.9, 81.6, 81.3, 77.7, 76.3, 75.0, 74.6, 73.4, 73.1, 72.6, 72.5, 72.3, 72.1, 60.3, 60.1, 59.9, 59.4.

*Anal.* Calc. for $C_{50}H_{78}O_{35}$: C, 48.46; H, 6.34. Found: C, 48.41; H, 6.42.

Fraction 2 was identified as a 6-*O*-(1-phenethyl)-βCD. N.m.r. spectra: $^1H$, δ 7.35–7.15 (m, 5 H, Ph), 4.45 (q, 1 H, *J* 6.4 Hz, $CH_3CH$), 1.26 (d, 3 H, *J* 6.4 Hz, $CH_3CH$); $^{13}C$, δ 144.1, 128.4, 127.3, 126.0, 102.7, 102.0, 101.9, 82.4, 81.7, 81.5, 81.4, 77.6, 73.4, 73.1, 73.0, 72.5, 72.2, 70.6, 67.4, 60.0, 24.3.

*Anal.* Found: C, 48.29; H, 6.36.

Fraction 3 was identified as a 6-*O*-(1-phenethyl)-βCD. N.m.r. data: $^1H$, δ 7.54–7.18 (m, 5 H, Ph), 4.49 (q, 1 H, *J* 6.1 Hz, $CH_3CH$), 1.28 (d, 3 H, *J* 6.1 Hz, $CH_3CH$); $^{13}C$, 144.1, 128.3, 127.1, 126.0, 102.3, 102.1, 102.0, 101.8, 82.6, 81.9, 81.7, 81.4, 77.0, 73.4, 73.1, 72.5, 72.2, 70.7, 67.5, 60.0, 23.7.

*Anal.* Calc. for $C_{50}H_{78}O_{35}\cdot H_2O$: C, 47.77; H, 6.41. Found: C, 47.96; H, 6.20.

Fraction 4 was identified as 3-*O*-(1-phenethyl)-β-CD. N.m.r. data $^1H$, δ 7.40–7.16 (m, 5 H, Ph), 5.30 (q, 1 H, *J* 6.1 Hz, $CH_3CH$), 1.45 (d, 3 H, *J* 6.1 Hz, $CH_3CH$);

$^{13}C$, $\delta$ 143.8, 128.1, 127.2, 126.3, 102.5, 102.2, 102.1, 101.6, 82.2, 81.9, 81.8, 81.6, 81.5, 78.4, 77.1, 74.4, 73.8, 73.1, 72.8, 72.5, 72.2, 60.0, 20.8.

*Anal.* Calc. for $C_{50}H_{78}O_{35}$: C, 48.46; H, 6.34. Found: C, 48.42; H, 6.18.

*Diazo(diphenyl)methane–β-cyclodextrin.* — The complex (1.38 g, 1.04 mmol; guest/host ratio, 1.0:1; 94 mol% diazo guest; generated via method B) was decomposed at 180–186° for 5 min. The ether-soluble products (77 mg, 41%) were analyzed by a combination of n.m.r. spectroscopy, g.l.c., and u.v. spectroscopy (azine was quantified by its absorption at 315 nm). The product distribution consisted (%) of diphenylmethane (46), benzophenone (10), benzhydrol (11), tetraphenylethane (1), and benzophenone azine (31). The mixture of *O*-diphenylmethyl-βCDs (520 mg, 0.40 mmol), 40%, isolated by flash reverse-phase chromatography of the water-soluble products, had $R_F$ 0.63 (5:4:3 *n*-BuOH–EtOH–$H_2O$) and was separated into two fractions by h.p.l.c., 36% (*T* 36 min) and 64% (42). N.m.r. data: $^1H$ [$(CD_3)_2SO$, $D_2O$], $\delta$ 7.49–7.18 (m, 10 H, 2 Ph), 6.63 (s, 1 H, $Ph_2CH$); $^{13}C$ [$(CD_3)_2SO$], $\delta$ 142.7, 141.6, 129.5, 128.5, 128.1, 126.9, 126.6, 102.6, 102.3, 102.2, 101.9, 100.7, 82.2, 81.9, 81.7, 81.3, 78.2, 75.2, 74.7, 73.4, 73.3, 73.1, 72.8, 72.6, 72.2, 72.1, 71.9, 60.5, 60.1, 59.9, 59.6.

*Anal.* Calc. for $C_{55}H_{80}O_{35}$: C, 50.77; H, 6.20. Found: C, 50.50; H, 6.37.

Fraction 2 was 6-*O*-diphenylmethyl-βCD. N.m.r. data: $^1H$, $\delta$ 7.33–7.11 (m, 10 H, 2 Ph), 5.40 (s, 1 H, $Ph_2CH$); $^{13}C$, $\delta$ 143.1, 142.9, 128.5, 128.4, 127.4, 127.3, 126.7, 126.5, 102.6, 102.2, 101.8, 82.9, 81.7, 81.5, 81.4, 81.3, 73.6, 73.2, 73.0, 72.6, 72.3, 70.7, 68.3, 60.1.

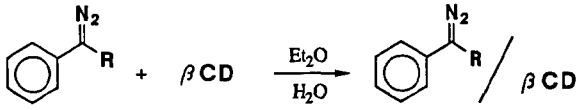
*Anal.* Found: C, 50.51; H, 6.48.

## RESULTS AND DISCUSSION

The diazo compounds **1a–1c** were generated by oxidation of the hydrazone and pyrolysis of the tosylhydrazone sodium salt. The second method usually gives diazo compounds of higher purity. Since the diazo compound is isolated in the pyrolysis reaction, its yield can be determined, and the stoichiometry of the inclusion step can be better controlled. This method cannot be used to make diazo(diphenyl)methane, which decomposes before it distills. The advantage with the hydrazone preparation is that the inclusion complex can be made safely on a relatively large scale, as the diazo compound is never isolated.

Inclusion complexes of βCD with diazo compounds **1a–1c** were prepared as described in the Experimental and the yields did not depend on the method used for diazo compound generation (Table I). The solids isolated were assumed to be inclusion complexes rather than co-precipitates based on literature precedent and on indirect evidence. For example, they could be pyrolyzed under vacuum and still retain the guest species. Since the preparation of these complexes involved several uncontrollable variables, the yields, guest distributions, and guest-to-host stoichiometries showed some variation.

The inclusion complexes were assayed for incorporation of the diazo com-




**1a** R = H
**1b** R = Me
**1c** R = Ph

**2a** R = H
**2b** R = Me
**2c** R = Ph

pound (Table I) by n.m.r. spectroscopy of solutions in $(CD_3)_2SO$. The guests-to-host ratio was determined from the ratio of integrated intensities of the signals for aromatic and anomeric protons. Also, the complexes were digested with acetic acid to give the corresponding acetates. However, since the diazo compound can decompose to other compounds, the yield of the acetate is a *lower* limit to the amount of diazo compound present. The mass balance of the products isolated after digestion with acetic acid accords with the extent of guest corporation determined by n.m.r. spectroscopy. The recovery was always >74%.

The diazo(phenyl)methanes **1a** and **1b** formed non-stoichiometric complexes with guest compositions of ~2:1 diazo compound to azine. Since the resulting solids were relatively static in composition, the formation of azine must have occurred during complexation through bimolecular reaction of the diazo compounds[12]. The ratios between the isomeric azines mimic those found in concentrated solution[13]. On the other hand, the diazo(diphenyl)methane **1c** gave a nearly pure 1:1 complex. For the most part, the n.m.r. data and the results of digestion with acetic acid gave similar distributions of guests. An exception was **2b**, where the digestion method indicated more ketone and less azine than did the n.m.r. data. For **2b**, the azine was converted into the corresponding carbonyl compound by the digestion process. The total relative amounts of azine and acetophenone determined by the two methods were similar.

TABLE I

SYNTHESIS OF INCLUSION COMPLEXES

| *Diazo compound* | *Method*[a] | *Yield (%)* | *Guest/host ratio* | *Relative % yield of included guests from HOAc digestion*[b] | | |
|---|---|---|---|---|---|---|
| | | | | *PhRC=O* | *PhRC=N₂* | *(PhRC=N-)₂* |
| $PhHCN_2$ | A | 60 | 0.9 | [c] ([c]) | 62 (59) | 20 (22) |
| $PhHCN_2$ | B | 62 | 0.5 | 4 ([c]) | 78 (65) | 8 (7) |
| $PhHCN_2$ | B | 26 | 0.9 | 6 ([c]) | 23 (34) | 6 (7) |
| $PhMeCN_2$ | A | 93 | 1.3 | 26 (1) | 67 (61) | 7 (38) |
| $PhMeCN_2$ | A | 73 | 0.4 | 38 (3) | 43 (34) | 19 (56) |
| $PhMeCN_2$ | B | 69 | 0.8 | 21 (4) | 65 (57) | 15 (39) |
| $Ph_2CN_2$ | A | 96 | 1.0 | 7 (3) | 93 (92) | [d] (<5) |

[a]A, pyrolysis of the tosylhydrazone sodium salt; B, oxidation of the hydrazone. [b]Determined by g.l.c. and n.m.r. spectroscopy (in parenthesis). [c]Too small to detect. [d]Cannot be determined by this technique.

TABLE II

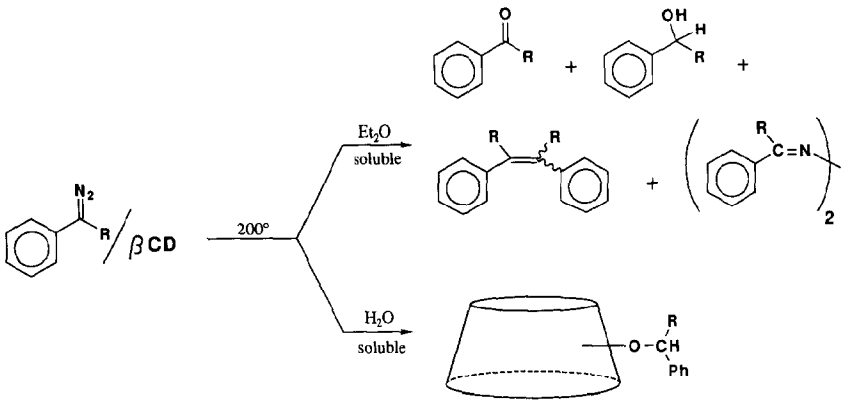
PYROLYSIS OF INCLUSION COMPLEXES

| *Diazo complex (guest:host, % diazo guest)* | *Temp. (°)* | *% Yield-recovery of $Et_2O$-soluble products (%)* | *Recovery % yield-recovery of $Et_2O$-soluble products* | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | *$PhRCH_2$* | *$PhRC{=}O$* | *$(PhRC{=})_2$* | | *$(PhRC{=}N{-})_2$* | *Other* |
| | | | | | cis | trans | | |
| $PhHCN_2 \cdot \beta CD$ (0.9, 78) | 185 | 84 | [a] | [a] | 19 | 7 | 53 | [b] |
| $PhMeCN_2 \cdot \beta CD$ (1.3, 65) | 186 | 52 | [a] | 21 | [a] | <1 | 50 | [c] |
| $Ph_2CN_2 \cdot \beta CD$ (1.0, 93) | 183 | 41 | 46 | 10 | <3 | | 31 | [d] |

[a]Too small to detect. [b]21% of deoxybenzoin. [c]27% of *trans*- and 1% of *cis*-1-methyl-1,2-diphenylcyclopropane. [d]11% of benzhydrol and 1% of 1,1,2,2-tetraphenylethane.

The diazo compounds in complexes **2a–2c** were decomposed by pyrolysis at 180–200°. Under these conditions, the elimination of $N_2$ to form the carbenes should be rapid[12]. Indeed, the complexes lost their characteristic coloration within 5 min. Once formed, the carbenes can rearrange, react with other guest species, or react with $\beta$CD[14]. The distributions of products, determined using g.l.c. and n.m.r. spectroscopy, are reported in Table II and given as yield-recoveries because some of the products were formed by reactions of the diazo compound, whereas others were present in the complex before pyrolysis. More ether-soluble products were recovered with the smaller diazo compounds in **1a** and **1b**, but these complexes are composed of about one-third azine. The distributions of products resemble those for the thermolysis of diazo compounds in isotropic solution[12], with some notable exceptions. Azine was formed in significant proportion from each complex, and was the main product from thermolysis in solution. The unusual products included deoxybenzoin from **2a**, *trans*-1,2-diphenylcyclopropane from **2b**, and diphenylmethane from **2c**. Deoxybenzoin results from the reaction of **1a** with benzaldehyde, formed[14] by the reaction of the carbene with $O_2$. The *trans*-1,2-diphenylcyclopropane resulted from a 1,3-dipolar cycloaddition between **1b** and styrene, formed from the carbene by a 1,2-hydrogen shift. The stereoselectivity for the *trans* isomer was much greater from **2b** than from thermolysis of **1b** in styrene (19:1 *vs.* 2.5:1), and was similar to that (25:1) from the corresponding diazirine/$\beta$CD complex[7]. Diphenylmethane was produced from the triplet carbene by sequential abstractions of hydrogen[14]. The source of the hydrogen atom must be the $\beta$CD, although no corresponding CD products were isolated.

Pyrolysis of complexes **2a–2c** also afforded water-soluble $\beta$CD derivatives (See Scheme 1). Derivatives bearing aromatic groups could be separated from $\beta$CD using flash reverse-phase chromatography, whereas fractionation of the mono-




Scheme 1. Pyrolysis products from diazo compound/βCD complexes.

derivatized isomers was achieved by preparative reverse-phase h.p.l.c. Based on $^{1}H$- and $^{13}C$-n.m.r. data and combustion analyses, these products were identified as the isomeric O–H insertion products. Insertion into C–H or C–C bonds would convert the diazo carbon into an alkyl carbon. In the $^{13}C$-n.m.r. spectrum, an alkyl carbon should resonate upfield from 60 p.p.m., but no such signals were observed. Insertion into O–H bonds was the expected reaction[14] between the electrophilic carbenes and the CD. Insertion can occur into one of three different hydroxyl groups in βCD, so that three regioisomeric products are possible. In addition, the insertion reaction generates a new chiral center for **1b**, and two diastereomers are possible for each regioisomer. Pyrolysis of **2a** and **2b** produced all three regioisomeric insertion products, whereas **2c** gave only the C-2 and C-6 isomers.

The assignment of the regiochemistry is straightforward for the C-6 isomers. Etherification of HO-6 should shift the resonance of C-6 downfield by 8 p.p.m., and that of C-5 methine upfield by 2 p.p.m. The resonance of the shifted C-6 carbon can be identified through an attached proton test. All C-6 derivatives showed two $^{13}C$ resonances between 67 and 71 p.p.m. (Fig. 1).

The assignment of the regiochemistry with the other derivatives is more tentative. The downfield shifts of the resonances of the α-carbons of the ethers are not sufficient to distinguish between the C-2 and C-3 derivatives. Here, the upfield shifts of the resonances of the β-carbons are important: the C-2 derivatives show large shifts for C-1 and small shifts for C-4, whereas the C-3 derivatives show the opposite trend (Fig. 2). Such effects are observed in the structurally related mono-*O*-methylglucoses[15]. Although the two derivatives produced from **2a** could be separated only partially by h.p.l.c., the resonances could be assigned to each isomer. The number of aromatic resonances in the $^{13}C$-n.m.r. spectrum indicated a mixture of only two derivatives. The derivative eluted first was the C-2 isomer (ΔC-1 1.6, ΔC-4 −0.8 p.p.m.) and the later compound was the C-3 isomer (ΔC-1 0.9, ΔC-4 1.3 p.p.m.). In addition to the two C-6-substituted diastereomers, two

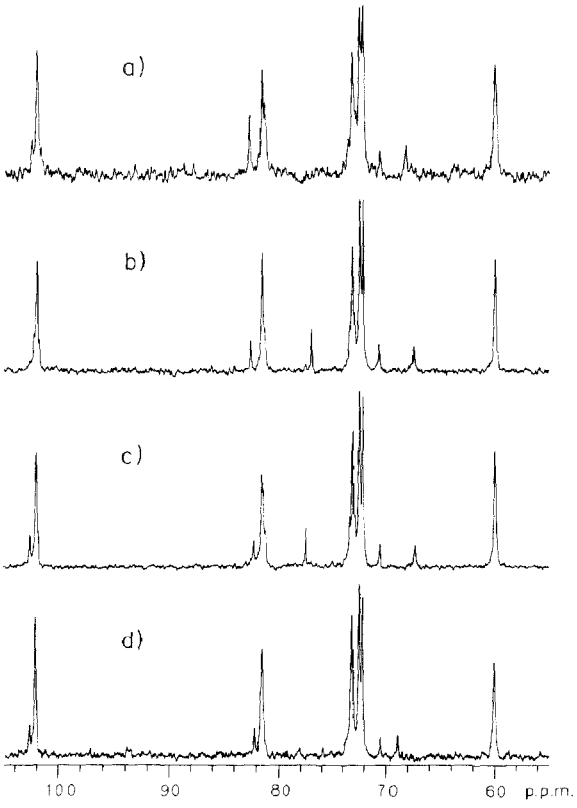



Fig. 1. $^{13}$C-N.m.r. spectra of 6-*O*-(R)-$\beta$-cyclodextrins: (a) R = $Ph_2CH$; (b) and (c) R = PhMeCH, diastereomers; (d) R = $PhCH_2$.

1-phenethyl derivatives were isolated from the pyrolysis of **2b**. These isomers had markedly different retention times, one being eluted before the C-6 isomers and one after. Each isomer showed downfield shifts for the resonance of C-4 of equal magnitude ($\Delta$ −0.8 p.p.m.), whereas the upfield shifts for the resonance of C-1 were nearly twice as large for the isomer eluted first ($\Delta$ 0.8 p.p.m.) then the later isomer ($\Delta$ 0.4 p.p.m.). Thus, the former is identified as a C-2 isomer, and the latter as a C-3 isomer. The order of elution, C-2 before C-3, is consistent with the benzyl derivatives above. These products appeared to be pure isomers by $^{13}$C-n.m.r. spectroscopy, which should be able to distinguish the other diastereomers. It appears that the chiral induction for the insertion reaction is large for the C-2 and C-3 regioisomers, whereas the ratio of C-6 diastereomers is only 1.4:1. The fact that other C-2 and C-3 diastereomers were not isolated does not mean that chiral induction is 100%, but rather that the amounts of these compounds were too small to accumulate during preparative h.p.l.c. Insertion on the secondary face of $\beta$CD places the carbene closer to a chiral center, so the difference in inductive effects is reasonable. Unlike **2a** and **2b**, only one regioisomer besides the C-6 derivative was

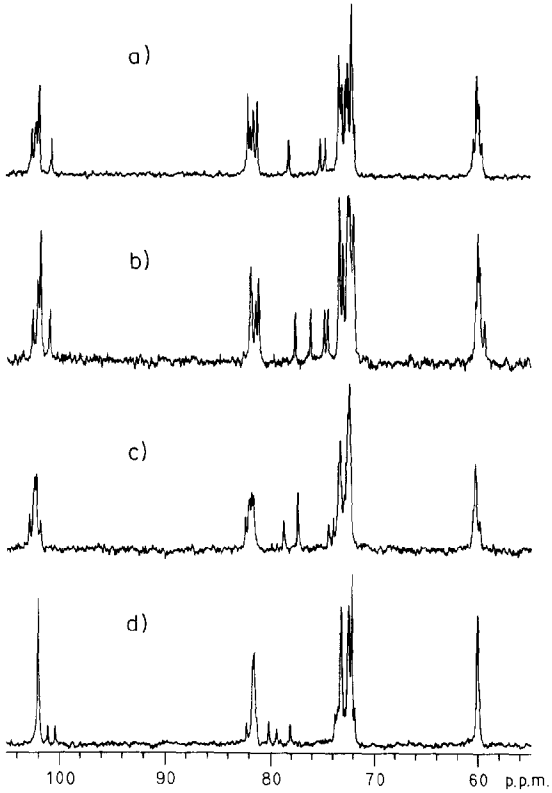



Fig. 2. $^{13}$C-N.m.r. spectra of 2- and 3-*O*-(R)-β-cyclodextrins: (a) 2, R = $Ph_2CH$; (b) 2, R = PhMeCH; (c) 3, R = PhMeCH; (d) 2 and 3, R = $PhCH_2$.

produced from **2c**, despite the fact that double the number of aromatic signals were observed. The phenyl groups in this derivative are diastereotopic, so that different chemical shifts are expected for the aromatic signals. The C-6 derivative also has diastereotopic phenyl rings, and doubled aromatic resonances are indeed observed. The differences in chemical shifts between corresponding resonances are smaller for the C-6 derivative than for the other derivative, since the phenyl groups are closer to a chiral center in the latter compound. The shift for the resonance of C-1 (Δ 1.2 p.p.m.) was greater than that for the resonance of C-4 (Δ −0.7 p.p.m.), and this derivative was identified as the C-2 derivative.

## CONCLUSIONS

The βCD showed "reaction vessel" effects on the guest–guest products. Diazo(diphenyl)methane (**1c**), which is bulkier than **1a** and **1b**, decomposed to produce mainly intramolecular products, whereas **1a** and **1b** produced more bimolecular products. Shape-selective effects were seen in the products from 1-

diazo-1-phenylethane, where the *trans*-cyclopropane was favored over the *cis* isomer. Some regioselectivity was observed in the guest–host products. The smaller diazo compounds produced all three regioisomers, whereas the larger diazo compound produced only the C-2 and C-6 isomers. The fact that the C-6 isomers were favored with the disubstituted diazo compounds **1b** and **1c** can be rationalized in terms of a "channel alignment" effect. With **1c**, for example, the two phenyl groups will tend to align the divalent carbon along the center axis of βCD, thereby hindering its scope for reaction. Since the HO-2 and HO-6 are most accessible from the inside of βCD, these are expected to be the sites of reaction.

The reactions of included carbenes with βCD are being studied further.

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