ELSEVIER

Carbohydrate Research 337 (2002) 1309–1312

CARBOHYDRATE RESEARCH

www.elsevier.com/locate/carres

Note

# Synthesis of novel cyclomaltoheptaose (β-cyclodextrin) derivatives containing the Ebselen key moiety of benzoisoselenazolone

Xiangliang Yang,* Qin Wang, Huibi Xu

*Department of Chemistry, Huazhong University of Science and Technology, Wuhan 430074, Hubei, PR China*

Received 19 November 2001; accepted 15 June 2002

**Abstract**

A series of five novel cyclomaltoheptaose (β-cyclodextrin) derivatives containing benzoisoselenazolone groups have been synthesized as glutathione peroxidase mimics. 

*Keywords:* Glutathione peroxidase; Enzyme mimics; β-Cyclodextrin; Cyclomaltoheptaose; Ebselen

Studies on model compounds of selenoenzymes will be beneficial to further elucidate the structure, the catalytic mechanism, and the chemical essence of the molecular recognition of the known selenoenzymes, such as glutathione peroxidase (GPx), which catalyzes the reduction of hydroperoxides by glutathione, and will possibly provide a clue to finding highly biologically active selenium compounds as potential chemotherapeutic agents. Reich and Jasperse reported that the oxidized form of GPx may have a cyclic selenenamide structure.[1] Various organoselenium compounds have been developed as GPx models so far.[2–5] *N*-Phenyl-1,2-benzoisoselenazolin-3(2*H*)-one (Ebselen), by far the best-known example, succeeds in mimicking the structure of the active site of GPx; however, it still suffers from poor water solubility and the lack of a substrate-binding site. Renson and co-workers[6] tried to incorporate a supplementary tetrahedral carbon into the heterocycle to enhance its solubility.

Cyclomaltooligosaccharides (cyclodextrins, CDs) have been extensively used to construct artificial enzymes due to their ability to form inclusion complexes and to give rise to regio- and stereospecificity with respect to the substrate and product during catalytic processing.[7] Furthermore, the functional or catalytic groups can be selectively introduced into CDs. Thus, by means of chemical modification on CDs, not only can catalytic groups be introduced into CDs at a specific site, but also the hydrophilic property of the cavity and the geometrical shape of substrate-binding site can be altered, leading to molecular recognition.[8,9] In recent years, several GPx mimics on the base of CDs have been investigated.[10–12] We have constructed and synthesized a new type of model compound of GPx by introducing the functional group of Ebselen[5]—benzoisoselenazolone into β-cyclodextrin (β-CD).

The novel model compounds were synthesized according to the processes outlined in Scheme 1. Sodium diselenide was obtained according to the modified method[13] of Klayman and Griffin.[14] Then, 2,2′-diselenodibenzoic acid[15] and *o*-chloroselenobenzoyl chloride[16] (**1**) were prepared as reported in the literature. The new key intermediate, methyl 3-oxo-1,2-benzoisoselenazole-3(2*H*)-propanoate (**2**) was synthesized through the reaction of compound **1** with methyl β-alaninate hydrochloride. 1,2-Benzoisoselenazol-3(2*H*)-one (**3**)[17] reacted with alkali to form the 1,2-benzoisoselenazol salt **4**.[17]

6-[(2-Aminoalkyl)amino]-6-deoxy-β-CDs (**6a**–**6d**) and 6-iodo-β-CD[18] (**7**) were prepared from 6-*O*-(*p*-tosyl)-β-CD (**5**) [19] with alkyl diamines and NaI, respectively (Scheme 2). Then 6-[1,2-benzoisoselenazol-3-(2*H*)-one]-β-CD (**8**) was prepared by the displacement of the iodo group in **7** by **4**. 6-[[2-(3-Oxo-1,2-benzoisoselenazole-3(2*H*)-propionylamino) alkyl]amino]-6-deoxy-β-CDs (**9a**–**9d**) were obtained by the amidation of compounds **6a**–**6d** with compound **2**.

* Corresponding author. Tel.: +86-27-87522520; fax: +86-27-87780456

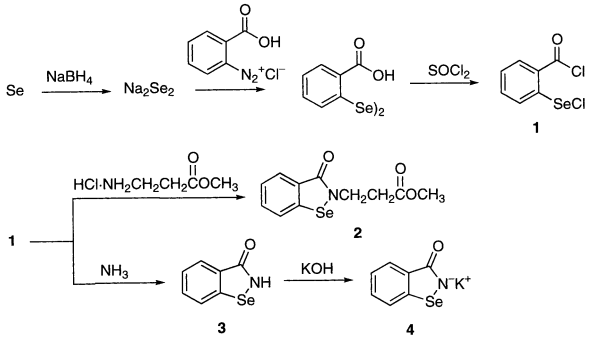
*E-mail address:* xlyang@public.wh.hb.cn (X. Yang).

0008-6215/02/$ - see front matter 
PII: S0008-6215(02)00158-1

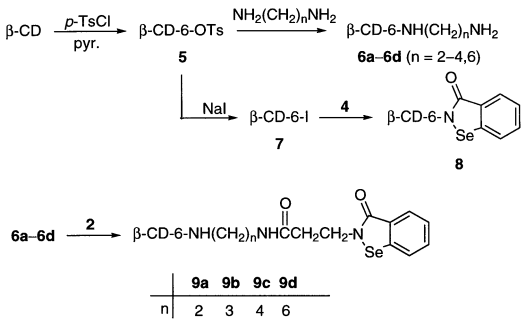
Compared with other previously reported GPx models such as those of Ebselen, these new compounds have following advantages: (1) better water solubility and (2) a flexible linkage between the β-CD moiety and the catalytic group. We now wish to report the synthesis of this series of five new β-CD derivatives bearing a benzoisoselenazolone groups. The GPx-like activities and substrate-recognizing abilities of these β-CD derivatives (**8** and **9**) have been confirmed and will be reported elsewhere.

## 1. Experimental

*Materials.*—β-CD (C.P.) was recrystallized three times from distilled water and dried in vacuum for 10 h at 90 °C. A saturated solution of *p*-toluenesulfonyl chloride (C.P.) in $Et_2O$ was successively washed with 5% aq NaOH solution twice and then with distilled water four times. The organic phase was dried with anhyd $MgSO_4$ and then filtered. The filtrate was dried in air to give white crystals of *p*-toluenesulfonyl chloride. Ethylenediamine and hexanediamine (A.R.) were purified on a fractionating column before use. Sodium borohydride, propanediamine and butanediamine were obtained from E. Merck and used directly. All solvents were pretreated as usual methods. Other commercially available reagents were used directly.




Scheme 1.




Scheme 2.

*General methods.*—$^1H$ and $^{13}C$ NMR spectra were recorded on a Bruker FT-500, a Varian XL-200 or a Bruker FT-AC 80 spectrometer with $Me_4Si$ as the internal standard ($^1H$ NMR) or with DSS as the external standard for $^{13}C$ NMR spectra. The chemical shifts are reported in ppm. IR spectra were obtained from Perkin–Elmer 983 infrared spectrometer. Elemental analyses were carried out on a Perkin–Elmer 2400II CHN elemental analyzer. Eluents for thin-layer chromatography (TLC) on GF-254 silica gel were as follows: (A) 3:3:2:5 ammonia–EtOAc–water–*n*-propanol; (B) 5:4:3 butanone–EtOH–water. A Sephadex G-15 column (Pharmacia, 30 × 1000 mm) and carboxymethyl cellulose CM-22 ion-exchange column (40 × 400 mm) were used to purify products. Silica gel flash-chromatograph separations were performed on a column (45 × 700 mm) packed with 1 cm of crude silica gel at the bottom with 20–25 cm fine silica gel mixed with petroleum ether added to the top. The progress of the reactions was monitored by TLC. Concentrations and evaporations were conducted in a vacuum.

*Methyl 3-oxo-1,2-benzoisoselenazol-3(2H)-propanoate* (**2**).—To a solution of **1** (2.79 g, 11 mmol) in dry $CH_2Cl_2$ (100 mL), methyl β-alaninate hydrochloride (1.54 g, 11 mmol, prepared by passing dry HCl into a solution of methyl β-alaninate in anhyd $CH_3OH$) was added. After the mixture was cooled to below 0 °C in an ice-salt bath, a solution of 5 mL $Et_3N$–10 mL $CH_2Cl_2$ was dropped in slowly. Then the mixture was stirred for 2 h at rt. The precipitate of $Et_3N{\cdot}HCl$ that formed was filtered and washed with $CH_2Cl_2$. The brownish–red filtrate was washed with 0.2 M HCl (3 × 50 mL), satd aq NaCl (2 × 50 mL) and satd aq $NaHCO_3$ (2 × 50 mL), and then evaporated to a small volume. The residue was mixed with crude silica gel to give a paste, then dried under an infrared lamp. The product was purified on a silica gel flash-chromatography column and eluted with a gradient of petroleum ether–EtOAc. The product was then recrystallized from petroleum ether–EtOAc to give primrose needles (1.3 g, 45%): mp 118.5–119 °C; IR (KBr): 1735, 1710, 1641, 1610, 1437, 1347, 1336, 1228, 1202, 1174, 1002, 736 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 7.2–8.2 (m, 4 H), 4.2 (t, 2 H), 3.7 (s, 3 H), 2.8 (t, 2 H). Anal. Calcd for $C_{11}H_{11}NO_3Se$: C, 46.51; H, 3.87; N, 4.93. Found: C, 46.37; H, 3.96; N, 4.84.

*6-[(2-Aminoethyl)amino]-6-deoxy-β-CD* (**6a**).—6-*O*-(*p*-Tosyl)-β-CD (**5**) (2.0 g, 1.5 mmol) was dissolved in ethylenediamine (20 mL) under an $N_2$ atmosphere. The mixture was stirred for 20 h at 70 °C, then evaporated. The primrose solid that formed was dissolved in a minimum amount of heated water, and then acetone (300 mL) was dropped in with stirring. The white powder was filtered off and again dissolved in warm water. The crude product was precipitated by addition of acetone, filtered off and again dissolved in a mini-

mum amount of water. The solution was applied to a column of CM-22 [$H^+$] ion-exchange resin. The column was washed with distilled water until there was no β-CD in the fractions as assayed by TLC, then the product was eluted out with 0.1 M aq NaCl. The fractions, including those of the product, were combined and concentrated, then desalted on a G-15 column eluted with distilled water. The product was precipitated from the aqueous solution by using acetone to give a white powder (1.2 g, 65%): TLC (A) $R_f$ 0.33; IR (KBr): 3350, 2921, 1630, 1460, 1400, 1371, 1326, 1292, 1202, 1153, 1075, 1025, 936, 838, 750, 702, 603, 578, 530 $cm^{-1}$; $^{13}C$ NMR ($D_2O$): $\delta$ 103.7, 103.4, 92.2, 82.8, 82.2, 79.4, 74.9, 74.6, 74.1, 73.7, 62.2, 61.8, 55.7, 50.1, 44.5. Anal. Calcd for $C_{44}H_{76}N_2O_{34}\cdot 2\ H_2O$: C, 43.56; H, 6.65; N, 2.31. Found: C, 43.69; H, 6.51; N, 2.40.

*6-[(2-Aminopropyl)amino]-6-deoxy-β-CD* (**6b**).—Compound **6b** 1.3 g (yield 71%) was prepared from compound **5** (2.0 g, 1.5 mmol) and propanediamine (20 mL) as generally described above, but differently in that the reaction time was 10 h: TLC (A) $R_f$ 0.35; IR (KBr) 3348, 2924, 1635, 1572, 1461, 1402, 1315, 1288, 1154, 1073, 1028, 992, 940, 744, 606, 527 $cm^{-1}$; $^{13}C$ NMR ($D_2O$): $\delta$ 103.6, 103.2, 98.1, 83.1, 82.9, 75.2, 74.5, 74.1, 62.1, 56.4, 49.6, 40.8, 27.3. Anal. Calcd for $C_{45}H_{78}N_2O_{34}\cdot 2\ H_2O$: C, 44.05; H, 6.74; N, 2.28. Found: C, 43.86; H, 6.57; N, 2.41.

*6-[(2-Aminobutyl)amino]-6-deoxy-β-CD* (**6c**).—Compound **6c** 1.4 g (yield 75%) was prepared from compound **5** (2.0 g, 1.5 mmol) and butanediamine (20 mL) as generally described above, but differently in that the reaction time was 10 h and the temperature of the reaction was 80 °C: TLC (A) $R_f$ 0.34; IR (KBr) 3350, 2924, 1632, 1465, 1402, 1324, 1292, 1154, 1074, 1022, 942, 748, 604, 580 $cm^{-1}$; $^{13}C$ NMR ($D_2O$): $\delta$ 104.4, 104.1, 84.1, 83.9, 75.1, 74.6, 73.9, 62.2, 52.3, 51.2, 43.6, 31.1, 29.4. Anal. Calcd for $C_{46}H_{80}N_2O_{34}\cdot 3\ H_2O$: C, 43.88; H, 6.88; N, 2.22. Found: C, 43.61; H, 6.78; N, 2.07.

*6-[(2-Aminohexyl)amino]-6-deoxy-β-CD* (**6d**).—Compound **6d** 1.3 g (yield 67%) was prepared from compound **5** (2.0 g, 1.5 mmol) and hexanediamine (20 mL) as generally described above, but differently in that the reaction time was 6 h and the temperature of reaction was 80 °C: TLC (A) $R_f$ 0.37; IR (KBr) 3350, 2930, 1634, 1462, 1400, 1324, 1285, 1152, 1072, 1024, 997, 938, 745, 702, 604, 580 $cm^{-1}$; $^{13}C$ NMR ($D_2O$): $\delta$ 103.7, 103.2, 84.3, 83.2, 75.8, 75.1, 74.2, 62.3, 50.2, 49.7, 41.4, 30.6, 28.1, 27.3, 26.7. Anal. Calcd for $C_{48}H_{84}N_2O_{34}\cdot 2\ H_2O$: C, 45.42; H, 6.99; N, 2.21. Found: C, 45.61; H, 6.82; N, 2.09.

*6-(1,2-Benzoisoselenazol-3(2*H*)-one)-β-CD* (**8**).—Compound **3** (0.48 g, 2.4 mmol) was dissolved in DMF (20 mL) in an ice bath, then 50% aq KOH (0.14 g, 2.4 mmol) was added with stirring for a moment. This mixture was added to the solution of β-CD-6-I (**7**) (1.0 g, 0.8 mmol) in DMF (50 mL). The reaction was carried out at 60 °C for 40 h under stirring, followed by evaporating the DMF. The brown residue was ground with acetone (50 mL). The solid was filtered and acetone was again added. This procedure was repeated twice. The resulting primrose powder was dissolved in water and precipitated by adding acetone. The white powder thus obtained was dried in vacuum to give the product (0.8 g, 78%): TLC (B) $R_f$ 0.34; IR (KBr) 3381, 2928, 1707, 1637, 1410, 1365, 1332, 1299, 1236, 1153, 1078, 1028, 943, 857, 754, 705, 638, 605, 578, 526, 486, 440 $cm^{-1}$; $^{13}C$ NMR ($D_2O$): $\delta$ 164.1, 138.5, 133.4, 130.6, 129.4, 128.8, 127.2, 103.3, 102.7, 98.3, 84.6, 83.7, 82.8, 75.6, 74.7, 74.1, 73.7, 62.1, 61.9. Anal. Calcd for $C_{49}H_{73}NO_{35}Se\cdot 2\ H_2O$: C, 43.56; H, 5.74; N, 1.04. Found: C, 43.72; H, 5.61; N, 0.87.

*6-[[2-(3-Oxo-1,2-benzoisoselenazole-3(2*H*)-propionyl-amino)ethyl]amino]-6-deoxy-β-CD* (**9a**).—To a solution of compound **6a** (1.0 g, 0.825 mmol) in DMF (50 mL), compound **2** (0.47 g, 1.65 mmol) was added. The reaction was carried out at 80 °C for 40 h with stirring. Then the solvent was distilled. The brown residue was dissolved in water and then filtered. The brown–red filtrate was decolorized with activated carbon. The colorless aqueous solution thus obtained was concentrated to a small volume, then applied to a CM-22 ion-exchange column ([$H^+$]) and eluted with a gradient of 0–0.15 M aq NaCl. The fractions were collected and assayed by TLC. The combined fractions that gave only one spot ($R_f$ 0.62, solvent A) were concentrated. The residue was further desalted on a G-15 column eluted with distilled water and freeze-dried to give a white powder (0.33 g, 27%): TLC (A) $R_f$ 0.62; IR (KBr) 3349, 2927, 2791, 2665, 2137, 1660, 1637, 1525, 1404, 1365, 1298, 1234, 1154, 1078, 1028, 942, 851, 753, 705, 646, 608, 575, 526, 438 $cm^{-1}$; $^{13}C$ NMR ($D_2O$): $\delta$ 171.2, 166.1, 139.2, 132.4, 130.2, 129.1, 126.3, 124.5, 103.7, 103.1, 97.8, 84.2, 83.8, 82.6, 75.4, 75.1, 74.8, 73.6, 61.3, 59.2, 56.2, 51.4, 47.8, 42.1, 36.3. Anal. Calcd for $C_{54}H_{83}N_3O_{36}Se\cdot 2\ H_2O$: C, 44.27; H, 5.98; N, 2.87. Found: C, 44.15; H, 5.84; N, 2.69.

*6-[[2-(3-Oxo-1,2-benzoisoselenazole-3(2*H*)-propionyl-amino)propyl]amino]-6-deoxy-β-CD* (**9b**).—Compound **9b** 0.37 g (yield 31%) was prepared from compound **6b** (1.0 g, 0.815 mmol) as generally described above: TLC (A) $R_f$ 0.64; IR (KBr) 3353, 2928, 1682, 1654, 1579, 1407, 1364, 1328, 1233, 1203, 1153, 1079, 1030, 942, 845, 753, 704, 681, 647, 606, 576, 527, 486, 444 $cm^{-1}$; $^{13}C$ NMR ($D_2O$): $\delta$ 172.1, 166.0, 139.2, 136.2, 133.8, 130.7, 129.5, 127.2, 103.3, 102.7, 99.2, 84.6, 82.2, 74.1, 73.6, 72.9, 70.4, 61.2, 59.3, 50.4, 47.6, 38.8, 37.2, 31.3. Anal. Calcd for $C_{55}H_{85}N_3O_{36}Se\cdot 2\ H_2O$: C, 44.66; H, 6.06; N, 2.84. Found: C, 44.48; H, 5.94; N, 2.67.

*6-[[2-(3-Oxo-1,2-benzoisoselenazole-3(2H)-propionyl-amino)butyl]amino]-6-deoxy-β-CD* (**9c**).—Compound **9c** 0.42 g (yield 35%) was prepared from compound **6c** (1.0 g, 0.794 mmol) as generally described above: TLC (A) $R_f$ 0.60; IR (KBr) 3350, 2928, 2149, 1706, 1637, 1559, 1419, 1365, 1300, 1229, 1154, 1078, 1029, 942, 845, 753, 704, 607, 579, 527, 486, 442 $cm^{-1}$; $^{13}C$ NMR ($D_2O$): $\delta$ 171.4, 166.5, 139.4, 135.4, 133.6, 130.3, 129.2, 126.4, 103.6, 103.2, 98.4, 85.6, 83.1, 75.2, 74.6, 73.3, 73.1, 61.4, 58.6, 52.6, 47.4, 38.4, 36.4, 33.7, 32.6. Anal. Calcd for $C_{56}H_{87}N_3O_{36}Se{\cdot}3\ H_2O$: C, 44.51; H, 6.20; N, 2.78. Found: C, 44.67; H, 6.04; N, 2.62.

*6-[[2-(3-Oxo-1,2-benzoisoselenazole-3(2H)-propionyl-amino)hexyl]amino]-6-deoxy-β-CD* (**9d**).—Compound **9d** 0.42 g (yield 35%) was prepared from compound **6d** (1.0 g, 0.788 mmol) as generally described above: TLC (A) $R_f$ 0.71; IR (KBr) 3355, 2929, 2155, 1704, 1657, 1533, 1407, 1364, 1298, 1231, 1202, 1153, 1078, 1029, 942, 857, 754, 705, 643, 606, 578, 528, 487, 444 $cm^{-1}$; $^{13}C$ NMR ($D_2O$): $\delta$ 170.2, 166.1, 138.6, 134.1, 129.5, 127.2, 126.4, 124.5, 104.3, 103.8, 98.2, 85.6, 83.2, 75.4, 74.3, 74.2, 69.2, 62.6, 62.0, 56.2, 50.0, 43.8, 39.8, 32.2, 30.0, 27.4, 26.8. Anal. Calcd for $C_{58}H_{91}N_3O_{36}Se{\cdot}2\ H_2O$: C, 45.79; H, 6.29; N, 2.76. Found: C, 45.57; H, 6.12; N, 2.58.

## References


1. Reich, N. J.; Jasperse, C. P. *J. Am. Chem. Soc.* **1987**, *109*, 5549–5551.
2. Mugesh, G.; DuMont, W. W. *Chem. Eur. J.* **2001**, *7*, 1365–1370.
3. Mugesh, G.; Singh, H. B. *Chem. Soc. Rev.* **2000**, *29*, 347–357 and references therein.
4. Erdelmeier, I.; Tailhan-Lomont, C.; Yadan, J. C. *J. Org. Chem.* **2000**, *65*, 8152–8157.
5. Sies, H. *Free Radical Biol. Med.* **1993**, *14*, 313–323.
6. Jacquemin, P. V.; Christiaens, L. E.; Renson, M. J. *Tetrahedron Lett.* **1992**, *33*, 3863–3866.
7. Saenger, W. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 344–362.
8. Liu, Y.; You, C. *Chem. J. Chin. U.* **2001**, *22*, 591–597 and references therein.
9. Breslow, R. *Acc. Chem. Res.* **1995**, *28*, 146–153 and references therein.
10. Ren, X. J.; Yang, L. Q.; Liu, J. Q.; Su, D.; You, D. L.; Liu, C. P.; Zhang, K.; Luo, G. M.; Mu, Y.; Yan, G. L.; Shen, J. C. *Arch. Biochem. Biophys.* **2001**, *387*, 250–256.
11. Liu, J. Q.; Luo, G. M.; Ren, X. J.; Mu, Y.; Bai, Y.; Shen, J. C. *Biochim. Biophys. Acta–Protein Struct. M* **2000**, *1481*, 222–228.
12. Ma, X. Y.; Wu, Y. H.; Ding, L.; Zhao, D. Q.; Ni, J. Z.; Liu, Y. *Chem. J. Chin. U.* **1999**, *20*, 1163–1167.
13. Yang, X. L.; Wang, Q.; Tao, Y. H.; Yao, S.; Xu, H. B. *Chin. J. Inorg. Chem.* **2001**, *17*, 905–907.
14. Klayman, D. L.; Griffin, T. S. *J. Am. Chem. Soc.* **1973**, *95*, 197–199.
15. Kamigata, N.; Iizuka, H.; Izuoka, A.; Kobayashi, M. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 2179–2183.
16. Renson, M; Piette, J. L. *Bull. Soc. Chim. Belg.* **1964**, *73*, 507–517.
17. Dallacker, F.; Peisker, A. *Chem. Z.* **1991**, *115*, 135–139.
18. Bonomo, R. P.; Cucinotta, V.; D'Alessandro, F.; Impellizzeri, G.; Maccarrone, G.; Vecchio, G.; Rizzarelli, E. *Inorg. Chem.* **1991**, *30*, 2708–2713.
19. Matsui, Y.; Okimoto, A. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 3030–3034.