Available online at www.sciencedirect.com

ScienceDirect

Mendeleev Commun., 2023, **33**, 622–623

Mendeleev
Communications

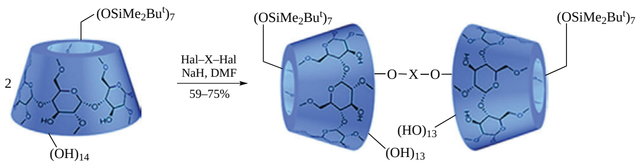
Cyclodextrin dimers connected with linkers through the secondary hydroxy groups

Mikhail K. Grachev,* Galina I. Kurochkina and Natalia V. Kutyasheva

Moscow Pedagogical State University, 129164 Moscow, Russian Federation. E-mail: mkgrachev@yandex.ru

DOI: 10.1016/j.mencom.2023.09.010

The simple synthesis of cyclodextrin dimers connected with linkers through the secondary hydroxy groups involves TBS protection of the primary hydroxy groups followed by linking with α,ω-dihalo aliphatic compounds. The dimers thus obtained may be of interest as molecular hosts in pharmaceutics, cosmetics and biomedicine.



Keywords: cyclodextrins, dimers, guest molecules, host molecules, hydroxy groups, drugs, NMR spectroscopy.

It is known that α-, β-, and γ-cyclodextrins (CDs, Figure 1) are unique objects which find use in various fields of science and technics.[1,2] The main interest in cyclodextrins is caused by their cyclic structure and the presence of internal hydrophobic cavity capable of forming host–guest inclusion compounds with various organic substrates. These CD properties especially attract attention in pharmacology for their use as molecular drug containers. Such incapsulation usually enhances bioaccessibility, solubility in water and protects drugs from biodegradation.

Among CD derivatives, their dimers (oligomers) would contain two (or more) internal CD cavities in one molecule. As a result, their spatial proximity and some other properties should have an increased so-called cooperative (not additive) effect toward the inclusion of various guests, which allows one to define them as a new class of supramolecular structures.[3,4] A little-known but important aspect of the application of dimeric cyclodextrins is that they can be represented as so-called bolaamphiphiles, *i.e*., amphiphilic molecules with two hydrophilic groups at the ends of the relatively long hydrophobic hydrocarbon chain. The presence of the second hydrophilic head dramatically increases the solubility in water and increases the critical concentration of the micelle formation, which promotes these bolaamphiphiles to form ensembles in water, *e.g*., spheres, cylinders, disks, and vesicles. Previously, we suggested simple and reliable methods for obtaining dimeric CDs connected with linkers at the primary hydroxy groups and studied their chemical behavior.[5]

In the present work we suggest the simple way for the synthesis of CD dimers connected with linkers through the secondary hydroxy groups. In comparison with those connected through the primary hydroxy groups, such derivatives are documented in a lesser extent because of the more complex route of their synthesis due to the necessity to protect the primary hydroxy groups. At the same time, these derivatives often show better chelation of ditopic ligands due to a wider input from the side of the secondary hydroxy groups.[4,6] With this in mind, the reaction between silyl-protected CD derivative **1**[7] and various difunctional derivatives **2a–d** afforded cyclodextrin dimers **3a–d** with linkers through the secondary hydroxy groups (Scheme 1). Activation of the secondary hydroxy groups was performed by the application of NaH in DMF. It is known[8] that the secondary hydroxy groups at C^2 due to stabilization of hydroxide anion by the hydrogen bond with the adjacent secondary hydroxy group at C^3 and due to electron accepting action of the adjacent acetal group are more acidic than those at C^3 (see Figure 1). This provides their deprotonation with the

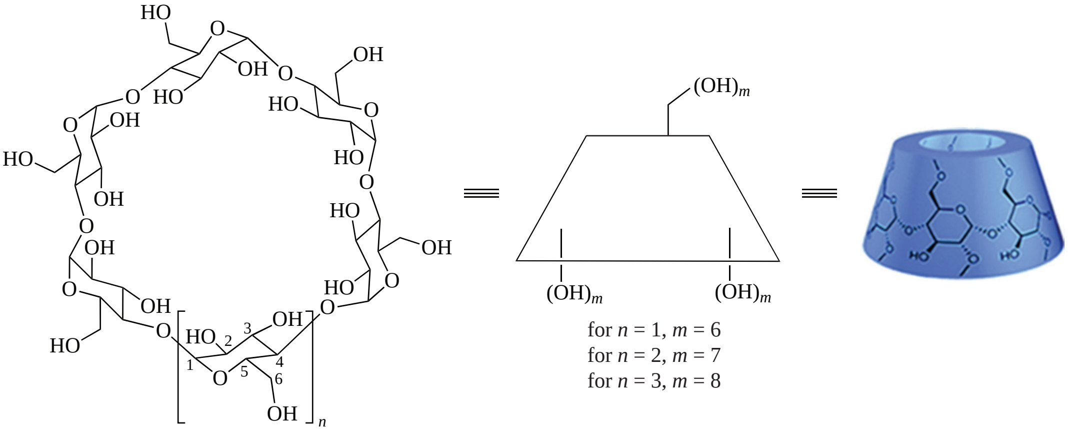
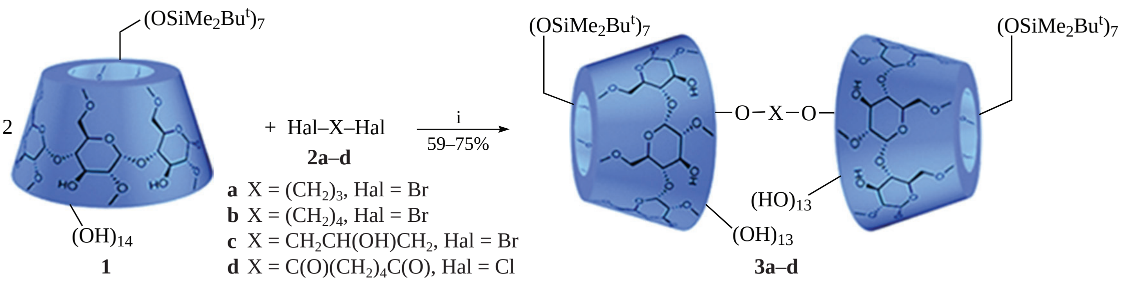


Figure 1 Chemical structure of α-, β-, and γ-cyclodextrins (n = 1, 2, 3, respectively).



Scheme 1

formation of mostly C^2-positioned oxy anions which then would attack electrophilic agents **2a–d**.

The structure of thus obtained products **3a–d** was confirmed by ^{1}H and ^{13}C NMR spectroscopy. The OH proton positions were identified by their considerable shift (by 0.3–0.8 ppm) at elevated temperature (80 °C). The signal assignment of compounds **3a–d** was additionally confirmed by 2D NMR spectra of homo- (HOMOCOR {^{1}H–^{1}H}) and heteronuclear (HETCOR {^{1}H–^{13}C}) correlations.

Previously, we have discovered that cyclodextrin derivatives connected with ether[5] or ester[9] bond at the primary hydroxy groups during the formation of inclusion compounds with aromatic monocarboxylic acids unexpectedly underwent slight hydrolysis of ether or ester bonds due to the inclusion of an acid (guest) into the cyclodextrin cavity. Taking that fact into consideration, in this work dimeric derivatives **3b**,**d** linked through ether (**3b**) or ester (**3d**) bonds were studied in the formation of inclusion compounds with benzoic acid under the same experimental conditions. It turned out that, according to ^{1}H NMR, these inclusion compounds with benzoic acid were formed without hydrolysis of ether/ester bonds. Thus, as regards the formation of inclusion compounds, dimeric β-cyclodextrin derivatives connected with linkers through the secondary hydroxy groups, essentially differ from those linked through the primary hydroxy groups. This circumstance widen their opportunities to be used as molecular containers (hosts) for the solution of many tasks in the field of pharmaceutics, biomedicine, and cosmetics.[10]

This paper was prepared according to scientific investigations of new laboratories under the guidance of young prospective investigators within the framework of program realization of strategic academic leadership ‘Priority-2030’: ‘Investigation of waste utilization of natural origin for the purpose of practical utilization of obtained products’.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2023.09.010.

References

1 *Cyclodextrin Fundamentals, Reactivity and Analysis*, eds. S. Fourmentin, G. Crini and E. Lichtfouse, Springer, 2018.
2 M. V. Papezhuk, V. A. Volynkin and V. T. Panyuskin, *Russ. Chem. Bull*., 2022, **71**, 430.
3 Y. Liu and Y. Chen, *Acc. Chem. Res.*, 2006, **39**, 681.
4 M. K. Grachev, I. V. Terekhova, D. A. Shipilov, N. V. Kutyasheva and E. Y. Emelianova, *Russ. J. Bioorg. Chem.*, 2020, **46**, 14 (*Bioorg. Khim*., 2020, **46**, 18).
5 N. V. Kutyasheva, G. I. Kurochkina, K. K. Ilinich and M. K. Grachev, *Macroheterocycles/Makrogeterotsikly*, 2022, **15**, 123.
6 J. M. Casas-Solvas, I. Quesad-Soriano, D. Carreño-Gázquez, J. J. Giménez-Martínez, L. Garcia-Fuentes and A. Vargas-Berenguel, *Langmuir*, 2011, **27**, 9729.
7 P. Fügedi, *Carbohydr. Res*., 1989, **192**, 366.
8 F. A. Menger and M. A. Dilany, *Tetrahedron Lett*., 1985, **26**, 267.
9 N. V. Kutyasheva, G. I. Kurochkina, V. V. Glushko and M. K. Grachev, *Russ. J. Gen. Chem*., 2021, **91**, 1070 (*Zh. Obshch. Khim*., 2021, **91**, 959).
10 *Cyclodextrins in Pharmaceutics, Cosmetics, and Biomedicine: Current and Future Industrial Applications*, ed. E. Billensoy, Willey, Hoboken, NJ, 2011.

Received: 9th February 2023; Com. 23/7098