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Asymmetric Induction in Intramolecular *meta* Photocycloaddition: Cyclodextrin-Mediated Solid-Phase Photochemistry of Various Phenoxyalkenes

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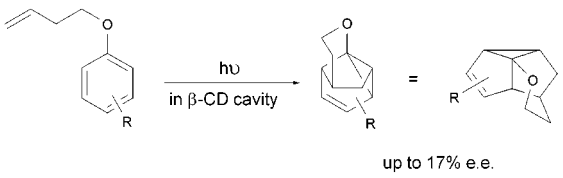
ABSTRACT



An approach to the asymmetric intramolecular *meta* photocycloaddition of phenoxyalkenes is described. The *β*-cyclodextrin complexes of several phenoxyalkenes have been synthesized and irradiated in the solid phase. The effect of the CD-hosting on the regio- and enantioselectivity is discussed. Values of ee up to 17% were obtained.

During the past decades several attempts have been carried out, with varying success, to induce chirality during photochemical conversions.[1,2] It is apparent that the level of interest in asymmetric photochemistry has not driven the available procedures to their ultimate limits compared to the area of the more conventional thermal processes. The application of cyclodextrin (CD) inclusion complexes in the modification of reactions in the ground state and of photochemical reactions has been intensively studied. However, their use in asymmetric photochemical reactions has been limited.[3,4] Examples include the photoisomerization of CD-complexed tropolone and 2-methoxytropone,[4a] the photodimerization of

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(1) For a detailed literature overview of the past decades, see: (a) Everitt, S. R. L.; Inoue, Y. *Molecular and supramolecular Photochemistry: Organic Molecular Photochemistry*; Ramamurthy, V., Schanze, K. S., Eds.; Marcel Dekker: New York, 1999; pp 71−130. (b) Ito, Y. *Synthesis* **1998**, 1−32. (c) Pete, J.-P. *Advances in Photochemistry*; Neckers, D. C., Volman, D. H., von Bünau, G., Eds.; John Wiley & Sons: New York, 1966; pp 135−216.

(2) Very recently excellent work has been published by Prof. V. Ramamurthy using chirally modified zeolite cages; see for example: (a) Shailaja, J.; Ponchot, J.; Ramamurthy, V. *Org. Lett.* **2000**, *2*, 937−940. (b) Joy, A.; Scheffer, J. R.; Ramamurthy, V. *Org. Lett.* **2000**, *2*, 119−121. (c) Joy, A.; Ramamurthy, V. *Chem. Eur J.* **2000**, *6*, 1287−1293. For work by Prof. F. Toda using inclusion crystals with an optically active host; see for example: (d) Toda, F.; Miyamoto, H.; Inoue, M.; Yasaka, S.; Matijasic, I. *J. Org. Chem.* **2000**, *65*, 2728−2732. (e) Tanaka, K.; Mochizuki, E.; Yasui, N.; Kai, Y.; Miyahara, I.; Hirotsu, K.; Toda, F. *Tetrahedron* **2000**, *56*, 6853−6865.

(3) (a) *Comprehensive Supramolecular Chemistry: Cyclodextrins*; Szejtli, J., Osa, T., Eds.; Pergamon: Elmsford, NY, 1966; Chapter 3. (b) Bortolus, P.; Monti, S. *Advances in Photochemistry: Photochemistry in Cyclodextrin Cavities*; Neckers, D. C., Volman, D. H., von Bünau, G., Eds.; John Wiley & Sons: New York, 1996; pp 1−133.

(4) (a) Takeshita, H.; Kumamoto, M.; Kouno, I. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1006−1009. (b) Tamaki, T.; Kokubu, T.; Ichimura, K. *Tetrahedron* **1987**, *43*, 1485−1494. (c) Aoyama, H.; Miyazaki, K.-I.; Sakamoto, M.; Omoto, Y. *Tetrahedron* **1987**, *43*, 1513−1518. (d) Rao, V. P.; Turro, N. J. *Tetrahedron Lett.* **1989**, *30*, 4641−4644. (e) Inoue, Yoshihisa; Kosaka, Satoru; Matsumotu, Kaoru; Tsuneishi, Hiroshi; Hakushi, Tadao; Tai, Akira; Nakagawa, Kazahura; Tong, Lin-Hui *J. Photochem. Photobiol., A* **1993**, *71*, 61−64.

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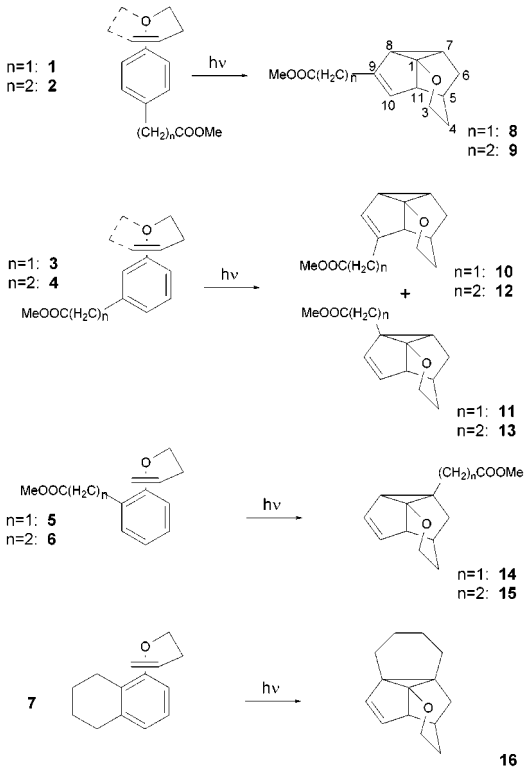
anthracene derivatives included in CD,[4b] the solid-state photoreaction of *N*,*N*-dialkylpyruvamide CD inclusion complexes,[4c] the photolysis of benzaldehyde absorbed in CD cavities,[4d] and the solid-state *Z*-*E* photoisomerization of a cyclooctene-β-cyclodextrin inclusion complex.[4e] The obtained ee's are generally low or not mentioned.

Here we report for the first time on the utility of β-cyclodextrin as a tool for asymmetric induction in the *meta* photocycloaddition of 4-phenoxybut-1-enes by solid complex formation with the chiral template β-cyclodextrin.

The intramolecular *meta* photocycloaddition is an intriguing one-step photochemical reaction accompanied by a dramatic increase in molecular complexity; therefore, it has attracted considerable interest for its potential as a convenient and versatile key step in the synthesis of complex polycyclic molecules.[5] A suitable asymmetric methodology would significantly enhance the applicability of this powerful reaction. To the best of our knowledge, so far no enantioselective version of this type of photoreaction has been described.

Recently, we extensively reported about the intramolecular *meta* and *ortho* photocycloaddition of 4-phenoxybut-1-enes, substituted in the arene residue with carbomethoxymethyl, and 2-carbomethoxyethyl groups (Scheme 1).[6]

Scheme 1. Intramolecular *meta* Photocycloaddition of 4-Phenoxybut-1-ene Derivatives



Focusing on the *meta* process several observations could be made: (a) in all cases, intramolecular *meta* photocycloaddition occurred regioselectively at the 2′,6′-positions of the arene to afford exclusively 1,5-bridged dihydrosemibullvalenes; (b) obviously the *para*-substituted bichromophores **1** and **2** provide only one *meta* photocycloadduct as a result of the inherent symmetry of the molecule; (c) in case of the *meta*-substituted photosubstrates **3** and **4** two different regioisomers were formed without notable regioselectivity; and (d) in contrast, completely regioselective *meta* photocycloaddition occurs upon irradiation of the *ortho*-functionalized **5**, **6**, and **7** as a result of steric hindrance in the transition state.

We will now describe our recent investigations in elaborating an enantioselective methodology for this *meta* photocycloaddition reaction. The photosubstrates **1**−**7** readily form solid complexes with β-cyclodextrin.[7] A warm (50 °C) solution of β-cyclodextrin (1.2 mmol) in water (85 mL) was added to the photosubstrate (0.4 mmol); the emulsion was sonicated for 15 min and stirred for 2 days at room temperature. A white precipitate was formed, which was isolated by centrifugation and decantation. Complexation was evident from their FT-IR and ^{1}H NMR spectra as indicated by the shift differences. The host/guest ratio was determined by UV spectroscopy after extraction of the photosubstrate from a known amount of complex with EtOH/H_2O (1:1). Depending on the substrate, 1:1 or 2:1 (host:guest) complexes were formed (Table 1). In the case of the 2:1 complexes the host is involved in a complexation with two CD moieties, hampering rationalization of the results. Irradiation of the solid cyclodextrin complexes was carried out in a cellophane envelope using low-pressure mercury arc lamps (300 nm, Rayonet Photochemical Reactor, type RS, Southern New England Ultraviolet Co., Middletown, Connecticut, USA) for

Table 1. Data and Results from β-CD-mediated Photoreactions

photosubstrate (guest)[a]	host:guest ratio[b]	regioselectivity[c]	ee[d] (%)
1	2:1	**8**	3
2	1:1	**9**	0
3	1:1	**10**:**11** = 1:3 (1:1)	17; 2
4	2:1	**12**:**13** = 1:1 (1:1.2)	9; 5
5	2:1	exclusively **14**	4
6	2:1	exclusively **15**	10
7	1:1	exclusively **16**	13

[a] Photosubstrates were stirred for 48 h in an aqueous solution of the CD, resulting in insoluble complexes. [b] Determined by UV spectroscopy after extraction with 1:1 EtOH/H_2O from a known amount of complex. [c] Product distribution obtained from "blank" irradiations is reported in brackets. [d] Determined by SFC as specified in ref 6.

(5) (a) Wender, P. A.; Siggel, L.; Nuss, J. M *Organic Photochemistry*; Padwa, A., Ed.; Marcel Dekker: New York, 1989; p 357. (b) Wender, P. A.; Dore, T. M. *Tetrahedron Lett.* **1998**, *39*, 8589−8592 and references cited therein.

(6) Vízvárdi, K.; Toppet, S.; Hoornaert, G. J.; De Keukeleire, D.; Bakó, P.; Van der Eycken, E. *J. Photochem. Photobiol., A* **2000**, *133*, 135−146. Yield values are not reported in this paper because of the inaccuracy of the mass measurements of the obtained small amounts of photoproducts. Also *ortho* addition takes place as was revealed by TLC. However, because of the instability of the products resulting from the initially formed *ortho* adducts these were not taken into account in the present study and the ratios to the *meta* cycloadducts were not determined.

(7) No solid inclusion complexes were obtained in trials with α-CD.

24 h with occasional agitation to ensure homogeneous photolysis of the sample. After irradiation, the material was suspended in water and extracted with diethyl ether. The ethereal solution was dried over $MgSO_4$ and concentrated under reduced pressure. Conversions were in the range of 55−82% determined by isolation of the unreacted starting material. The yields of the *meta* cycloadducts were considerably lower compared to those of the reaction performed in solution probably as a result of the irradiation of CD complexes in the solid state.[6] The photoproducts were purified by HPLC (Bio-Sil D90−10, 250 mm × 10 mm column) using hexane/ethyl acetate, 9:1 as the eluent. The enantiomeric excess was determined by Supercritical Fluid Chromatography (SFC).[8]

In the case of the "linear-type" bichromophores **1** and **2** forming, respectively, a 2:1 and 1:1 host:guest complex, the β-CD-assisted *meta* photocycloaddition reaction occurred with negligible or no enantioselectivity (Table 1). This is probably due to the position of the *para*-substituted bichromophore parallel with the C-7 axis of the CD(s) involved in the complexation, resulting in a relatively "loose" complex formation and quasi equal chance for the attack of the tether toward either "face" of the aromatic ring. On the contrary, in case of irradiation of the CD-complexed *meta*-substituted photosubstrate **3** (1:1 host:guest ratio) a significant ee of 17% was observed for the minor *meta* adduct **10**, while the major regioisomer **11** was isolated with an insignificant 2% ee. Compared to the irradition of the uncomplexed material, a remarkable change in regioselectivity was noticed: *meta* adduct **11** was formed in excess (**10**:**11** = 1:3 against the 1:1 ratio in the case of the uncomplexed material). On the basis of NOESY and ROESY ^{1}H NMR analysis a significant correlation has been found between the cyclodextrin H-3 nuclei and the isolated aromatic proton H-2′ and both tether hydrogens H-4 of the guest, indicating a close vicinity of the protons H-2′ and H-4 to the secondary rim of the CD as depicted in Figure 1. This provokes a possible rationalization

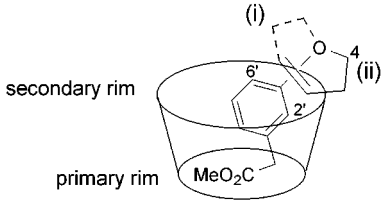


Figure 1. (i) Less hindered approach, low facial differentiation, 2% ee. (ii) More hindered approach, higher facial differentiation, 17% ee.

for the observed asymmetric induction. One could presume that this specific position of the guest in the chiral cavity can result in a more effective facial differentiation of the aromatic ring upon the approach of the tether from the CD-hindered direction (ii) affording **10** in a lower yield as compared to **11** but with higher enantiomeric excess of 17%. Indeed, during the less hindered (as H-6′ displays no NOESY or ROESY correlation with the cyclodextrin H-3 nuclei) attack (i), the chiral microenvironment of the host only exerted a very weak influence resulting in a 2% ee.

Upon irradiation of the *meta*-substituted photosubstrate **4**, much lower ee's are observed and the regioselectivity is unchanged compared to the irradiation of the uncomplexed material. As we are dealing here with a 2:1 host:guest complexation, the rationalization of these results is rather complicated, as is the case for the irradiation of the *ortho* substrates **5** and **6**, also involved in 2:1 complexation, showing ee's of 4% and 10%, respectively. Irradiation of the tetrahydronaphthol substrate **7** resulted in a single *meta* adduct **16** with 13% ee. The regioselectivity is in accordance with our earlier findings for the irradiation of the *ortho*-substituted substrates **5** and **6**.[6] Obviously, steric interactions arising from the tetramethylene ring fragment dictate a preferred orientation of the tether resulting in a single *meta* photocycloadduct. The observed enantioselectivity could not be rationalized by NOESY and ROESY experiments. However, we suppose that the bulkiness of substrate **7** could cause the formation of a more rigid CD-complex resulting in a tighter microenvironment with the CD. This gives a higher ee of 13%.

Cyclodextrins exhibit enantiomer recognition in complex formation with racemic compounds.[9] To rule out the possibility that the asymmetric induction observed in the photolysis of β-cyclodextrin complexes is due to optical resolution of racemic *meta* adduct formed during the reaction, racemic *meta* adduct **10** was complexed with β-cyclodextrin and the solid complex was suspended in water. The *meta* adduct obtained by extraction with diethyl ether showed no optical rotation.

Although the enantioselectivity obtained in the present study is low, considering the very few successful attempts for achieving asymmetry in photochemistry in general, the present results can be considered as a significant contribution toward the enantioselective *meta* photocycloaddition reaction. To the best of our knowledge no precedents have been described as yet for this type of reaction. For a better understanding a further study of substituent effects and the influence of the bulkiness of the substrate upon the asymmetric induction will be investigated. Experiments with modified cyclodextrins will be performed in due course.

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(8) The SFC separation was performed on an HP G1205A SFC (Hewlett-Packard) coupled to an HP 1050 DAD using Chiralpak AD L 250 mm × 4.6 mm i.d. (Daicel) semipreparative HPLC column. The elution was done with CO_2/methanol of varying ratios under supercritical conditions. Full details are given in: K. Desmet, K.; Sandra, P.; Vízvárdi, K.; Hoornaert, G. J.; Van der Eycken, E. *J. Microcolumn Sep.*, accepted for publication.

(9) (a) Bender, M. L.; Komiyama, M. *Cyclodextrin Chemistry*; Springer-Verlag: New York, 1978. (b) Tabushi, I. *Acc. Chem. Res.* **1982**, *15*, 66−72. (c) Ramamurthy, V.; Eaton, D. F. *Acc. Chem. Res.* **1988**, *21*, 300−306.(d) Ramamurthy, V. *Tetrahedron* **1986**, *42*, 5753−5839. (e) Breslow, R. *Science (Washington, D.C.)* **1982**, *218*, 532−537.