Photolabile calixarene-based rosette

Zaiguo Li, Huy Chiu, and Andrei G. Kutateladze

Abstract: A model calix[4]arene-based rosette carrying two alternating photocleavable dithianyl-hydroxy-methyl moieties and two benzophenonecarboxylates was synthesized and shown to be capable of photoinduced fragmentation, with efficiency comparable to that of the externally sensitized parent dithiane–benzaldehyde adducts.

Key words: photoinduced electron transfer, photofragmentation, calixarene, dithiane–carbonyl adducts.

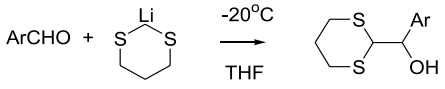
Résumé : On a effectué la synthèse d'une rosette modèle à base de calix[4]arène portant deux portions alternées de dithianyl-hydroxy-méthyle photoclivables et de deux benzophénonecarboxylates; on a démontré qu'il est possible d'en provoquer une fragmentation photoinduite avec une efficacité comparable à celle des adduits parents dithiane–benzaldéhyde sensibilités d'une façon externe.

Mots clés : transfert d'électron photoinduit, photofragmentation, calixarène, adduits dithiane–carbonyle.

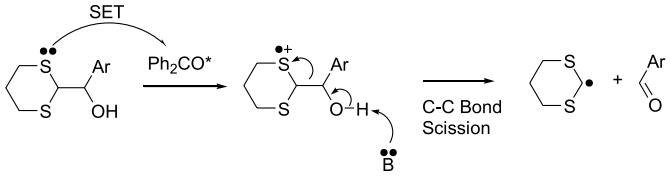
[Traduit par la Rédaction]

Introduction

Calixarenes modified at their upper or lower rim are often used as scaffolds for modular assembly of complex macromolecules. The relative rigidity of the calixarenic macrocycle makes it a spacer of choice for positioning various substituents and (or) molecular blocks in a daisy-wheel-like fashion. Specific examples range from ion-selective chelators and ionophores (1) to tethered polypeptides capable of protein surface recognition (2) to recognition-based sensing of other peptides (3), etc. We suggest that an attractive functional feature for such modular designs would be to assemble them by interconnecting the core scaffold and the auxiliary peripheral modules via photolabile tethers. This in essence is the approach that we have been developing based on the recently discovered photofragmentation reaction of α-hydroxyalkyl dithianes and related compounds in the presence of an electron transfer sensitizer, such as benzophenone (4). These compounds are readily available through nearly quantitative lithiodithiane additions to carbonyl compounds — a reaction that was developed three decades ago by Corey and Seebach (5), and that over the years has been implemented in numerous successful synthetic procedures.

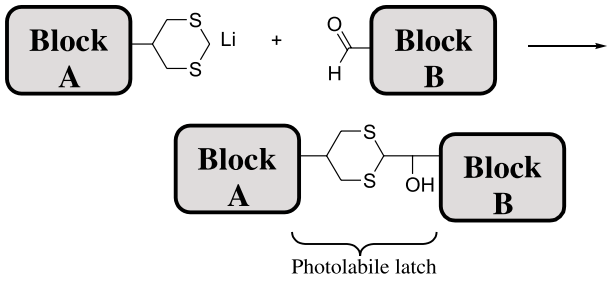


The photofragmentation is initiated by photoinduced electron transfer from the dithiane moiety to the excited triplet benzophenone, followed by mesolytic cleavage in the generated cation–radical (4).



Mechanistic aspects of similar fragmentations in cation–radicals containing other heteroatoms were studied by Arnold, Whitten, Maslak, and co-workers (6).

We use such dithiane–carbonyl adducts as photolabile "latches" that can hold together various molecular blocks, and are capable of releasing them upon photoirradiation (7).



In this communication, we report the synthesis of a model calixarene-based photocleavable rosette outfitted with an internal sensitizer, and its photoinduced fragmentation. Unsubstituted dithiane is used as a simple "model" of a macromolecular block that potentially can be attached to the calixarenic scaffold via dithianes substituted at position 5, for example 5-carboxy- or 5-hydroxymethyldithiane.

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This paper is dedicated to Professor Don Arnold.

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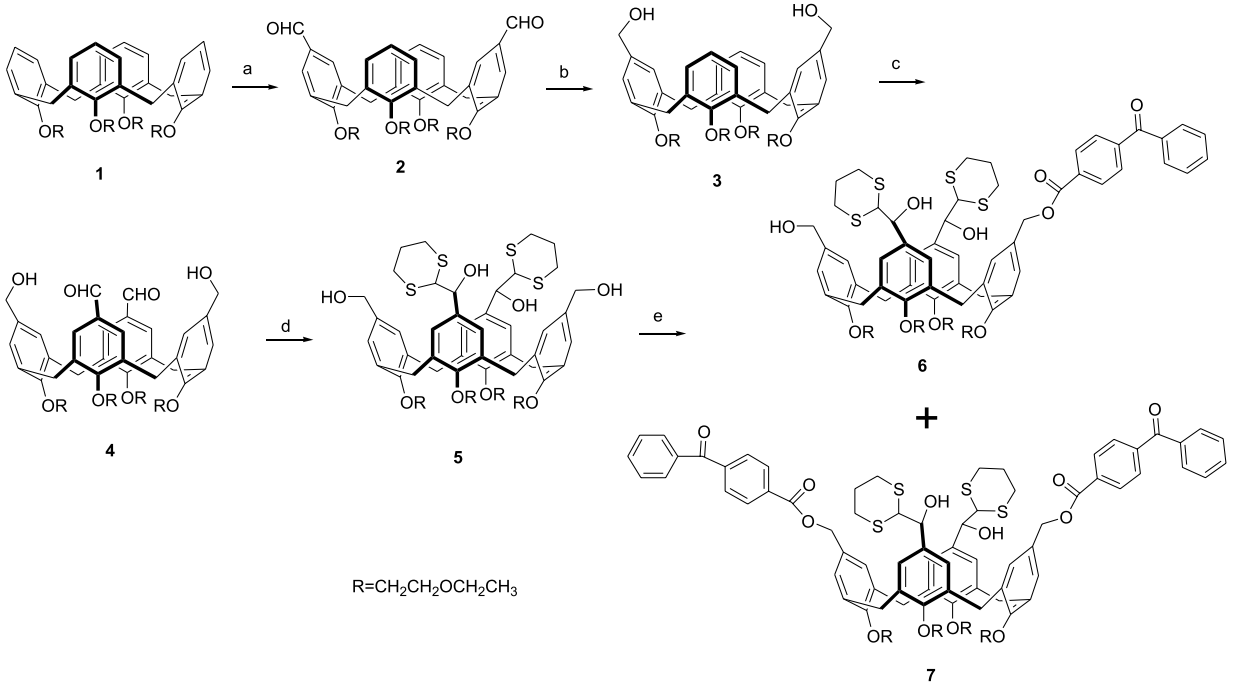
Scheme 1. (*a*) $CHCl_2OCH_3$–$SnCl_4$–$CHCl_3$, 46%; (*b*) $NaBH_4$–EtOH 86%; (*c*) $CHCl_2OCH_3$–$TiCl_4$–$CHCl_3$, 41%; (*d*) excess lithiated dithiane, THF, –78°C to r.t., 42%; (*e*) PhC(O)PhCOCl, Et_3N, CH_2Cl_2, 20 h (see text).



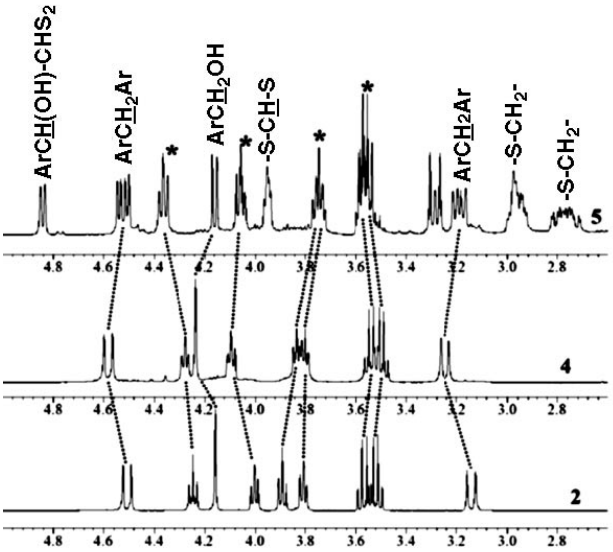
The overall synthetic scheme is presented below (Scheme 1). Commercially available calix[4]arene was tetraalkylated with 2-ethoxyethylbromide to give **1** and then bis-formylated according to the procedure by Arduini et al. (8) yielding **2**. The dialdehyde **2** was reduced with sodium borohydride and the formylation was repeated. The C_2-symmetric dialdehyde–diol **4** was reacted with excess lithiated dithiane to furnish bis-adduct **5** (42%).

Addition of dithianyl anion to dialdehyde **4** was expected to produce a pair of diastereomers. Given the large spatial separation of the chiral centers, we did not expect any diastereoselectivity and the NMR spectrum of bis-adduct **5** seems to corroborate this conclusion. As is shown in Fig. 1, the proton signal for the primary benzylic alcohols, which is a singlet in **4**, is represented by two separate peaks in **5** (4.17 and 4.15 ppm). Also, the calixarenic methylenes, Ar-CH_2-Ar (both sets of four "in" and four "out"), which are doublets in **1**–**4**, are represented by two sets of doublets each in the compound **5** (and **7**).[2]

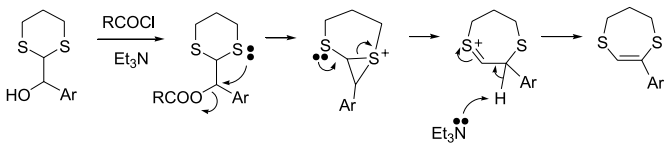
An alternative rationale for the observed doubling of the benzylic peaks is that **5** is a single diastereomer, but the crowded steric environment in it prevents free rotation of the dithianyl groups and they are caught in an unsymmetrical conformation, resulting in magnetically nonequivalent protons. Formation of only one diastereomer is, however, unlikely. We heated the sample of **5** in deuterated chloroform to 55°C and did not observe any coalescence of the benzylic signals in NMR. We, therefore, interpret the observed NMR spectrum as a 1:1 mixture of diastereomers. Both diastereomers are suitable for the assembly of the target photolabile rosettes. In this study we employed benzophenone-4-carboxylic acid as a tethered internal sensitizer. It was first converted into *p*-benzoylbenzoyl chloride via reaction with oxalyl chloride in dichloromethane and then cou-

[2] 5,17-Dihydroxymethyl-25, 26, 27, 28-tetrakis(2-ethoxyethoxy)calix[4]arene (**3**): ^{1}H NMR data (400MHz, $CDCl_3$): 6.89 (d, J = 8.0 Hz, 4H), 6.76 (t, J = 8.0 Hz, 2H), 6.40 (s, 4H), 4.51 (d, J = 13.2 Hz, 4H), 4.24 (t, J = 6.4 Hz, 4H), 4.16 (s, 4H), 4.00 (t, J = 5.6 Hz, 4H), 3.89 (t, J = 6.4 Hz, 4H), 3.81 (t, J = 5.6 Hz, 4H), 3.59–3.49 (m, 8H), 3.14 (d, J = 13.6 Hz, 4H), 1.98 (s, 2H), 1.24–1.16 (m, 12H). 5,17-Diformyl-11,23-dihydroxymethyl-25,26,27,28-tetrakis(2-ethoxyethoxy)calix[4]arene (**4**): 9.66 (s, 2H), 7.24 (s, 4H), 6.61 (s, 4H), 4.57 (d, J = 13.6 Hz, 4H), 4.27 (t, J = 6.4 Hz, 4H), 4.24 (s, 4H), 4.09 (t, J = 6.4 Hz, 4H), 3.83–3.77 (m, 8H), 3.56–3.46 (m, 8H), 3.24 (d, J = 13.6 Hz, 4H), 1.22–1.14 (m, 12H). Bis-adduct **5**: 7.23 (s, 2H), 7.15 (s, 2H), 6.66–6.62 (m, 4H), 4.84 (d, J = 7.3 Hz, 2H), 4.54 and 4.51 (2d, J = 12.4 Hz, 4H), 4.36 (t, J = 6.8 Hz, 4H), 4.16 (d, J = 7.3 Hz, 2H), 4.06 (t, J = 6.6 Hz, 4H), 3.97–3.92 (m, 4H), 3.77–3.72 (m, 4H), 3.61–3.50 (m, 8H), 3.31–3.27 (m, 4H), 3.21 and 3.17 (2d, J = 12.4 Hz, 4H), 3.00–2.71 (m, 8H), 2.13–1.90 (m, 4H), 1.22 (m, 12H). Monobenzoylated compound **6**: 8.21 (d, J = 8.1 Hz, 2H), 7.84 (d, J = 8.8 Hz, 2H), 7.77 (d, J = 8.8 Hz, 2H), 7.65 (t, J = 7.3 Hz, 1H), 7.52 (t, J = 7.3 Hz, 2H), 7.35 (d, J = 2.2 Hz, 1H), 7.29 (d, J = 2.2 Hz, 1H), 7.20 (d, J = 2.2 Hz, 1H), 7.06 (d, J = 2.2 Hz, 1H), 6.39–6.28 (m, 4H), 6.18 (d, J = 8.1 Hz, 1H), 4.76–4.70 (m, 2H), 4.50–4.43 (m, 4H), 4.36 (d, J = 7.3 Hz, 1H), 4.27–4.20 (m, 4H), 3.92–3.70 (m, 16H), 3.56–3.46 (m, 8H), 3.18–3.09 (m, 4H), 3.01–2.77 (m, 8H), 1.82–1.72 (m, 2H), 1.18–1.04 (m, 12H). Bis-benzoylated compound **7**: 8.24 (d, J = 8.8 Hz, 4H), 7.87 (d, J = 8.8 Hz, 4H), 7.8 (d, J = 8.8 Hz, 4H), 7.67 (t, J = 7.3 Hz, 2H), 7.54 (t, J = 7.3 Hz, 4H), 7.38 (d, J = 2.2 Hz, 2H), 7.32 (d, J = 2.2 Hz, 2H), 6.37 (d, J = 2.2 Hz, 2H), 6.27 (d, J = 2.2 Hz, 2H), 6.21 (d, J = 8.1 Hz, 2H), 4.74 (d, J = 8.1 Hz, 2H), 4.48 and 4.44 (2d, J = 13.2 Hz, 4H), 4.27 (m, 4H), 3.89–3.70 (m, 16H), 3.53 (m, 8H), 3.18 (d, J_1 = 13.2 Hz, 4H), 3.05–2.81 (m, 8H), 1.80–1.75 (m, 2H), 1.18 (t, J = 7.3 Hz, 6H), 1.10 (t, J = 7.3 Hz, 6H). MS (*m*/*z*): 1485.5 (MH^+), 1433.1, 1402.5, 1297.6, 1189.6, 1123.7, 1069.5, 1015.7, 967.6, 951.4, 897.7, 977.7, 209.0, 119.0.

Fig. 1. Comparison of ^{1}H NMR spectra ($CDCl_3$) for **2**, **4**, and **5**; signals of the protons belonging to ethoxyethoxy tails ($CH_3CH_2OCH_2CH_2O$ -) are marked by asterisks.



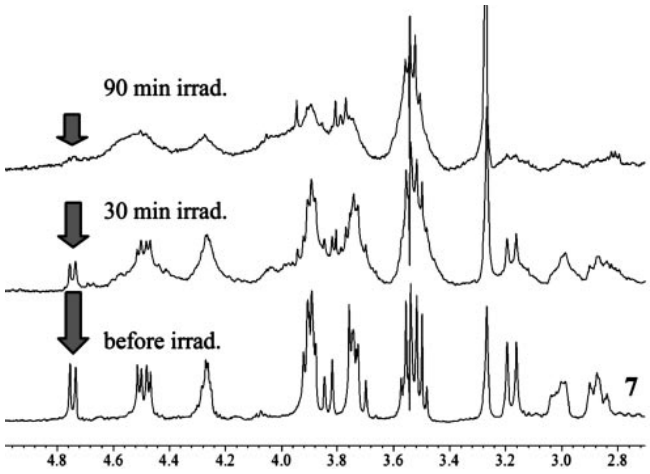
pled with alcohol **5** in the presence of triethylamine. We expected that the difference in reactivity between the primary benzylic and the more hindered secondary benzylic alcohols will ensure chemoselectivity. It appeared, however, that the difference in reactivities was not sufficient to completely shut off acylation of the latter. Judging by ^{1}H NMR, benzoylation produced several products. We speculate that acylation of the secondary alcohol groups may have triggered dehydrative ring expansion producing seven-membered dithiepines (9) and lowering the yield of the target rosette **7**.



Direct dicyclohexylcarbodiimide-mediated coupling of **5** with benzoylbenzoic acid did not improve the yield of the bis-adduct **7**. The presence of the carbonyl group in the sensitizer moiety precluded an alternative route to **7** via benzoylation of the diol **4** with the subsequent addition of dithianyl anion. Our attempt to implement this route produced a mixture of dithiane addition products to both formyl groups and also to benzophenone carbonyls. Successful synthesis of **7** was achieved via the acylation of **5** with *p*-benzoylbenzoyl chloride under partial (45%) conversion conditions. HPLC separation of the reaction mixture on a C-18 reversed phase column (MeCN–H_2O, 1:1) produced diester **7** (18% based on reacted **5**) and monobenzoylated adduct **6** (25%).

Having isolated the diastereomers **7**, we then proceeded with photochemical studies. Irradiation of **7** in acetonitrile

Fig. 2. Irradiation of **7** in CD_3CN.



with a medium pressure mercury lamp and Pyrex filter (300 nm cutoff) was monitored by ^{1}H NMR by following the disappearance of the benzylic dithianyl-C*H*-OH doublet. As shown in Fig. 2, the relative intensity of the doublet decreases with irradiation. In our previous work, we also followed the photofragmentation by NMR monitoring of the release of aromatic aldehydes (4). In the present study, while we see formyl singlets appearing in the NMR spectrum of the irradiated **7**, the aldehydes do not accumulate significantly upon extended photolysis. Our rationale is that the photoexcited benzophenone, being tethered in close proximity, oxidizes the liberated aldehyde. The overall efficiency of the self-sensitized photofragmentation of rosette **7** is comparable to that of a simple parent adduct of benzaldehyde and dithiane (quantum yield of about 0.12).

To rule out the involvement of calixarenic framework in sensitization of the dithiane–carbonyl fragmentation, we carried out a control experiment by irradiating tetra-alcohol **5**, which lacks the benzophenone-based sensitizing units. Irradiation of **5** under similar conditions (medium pressure mercury lamp, Pyrex filter) for 1 h produced no changes in the ^{1}H NMR spectrum of **5**, ruling out self-sensitization by the calixarene itself.

In summary, we have synthesized a model calixarene-based photolabile rosette capable of self-sensitized photofragmentation. Work is in progress in our laboratory to assemble functional rosettes with 5-substituted dithianes carrying macromolecular modules, for example, modules equipped with hydrogen bond-based elements of molecular recognition.[3]

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[3] Supplementary data may be purchased from the Depository of Unpublished Data, Document Delivery, CISTI, National Research Council Canada, Ottawa, ON K1A 0S2, Canada (http://www.nrc.ca/cisti/irm/unpub_e.shtml for information on ordering electronically).

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