Synthesis of (Homooxa)calixarene−Monoquinones through the “All-but-One” Methodology

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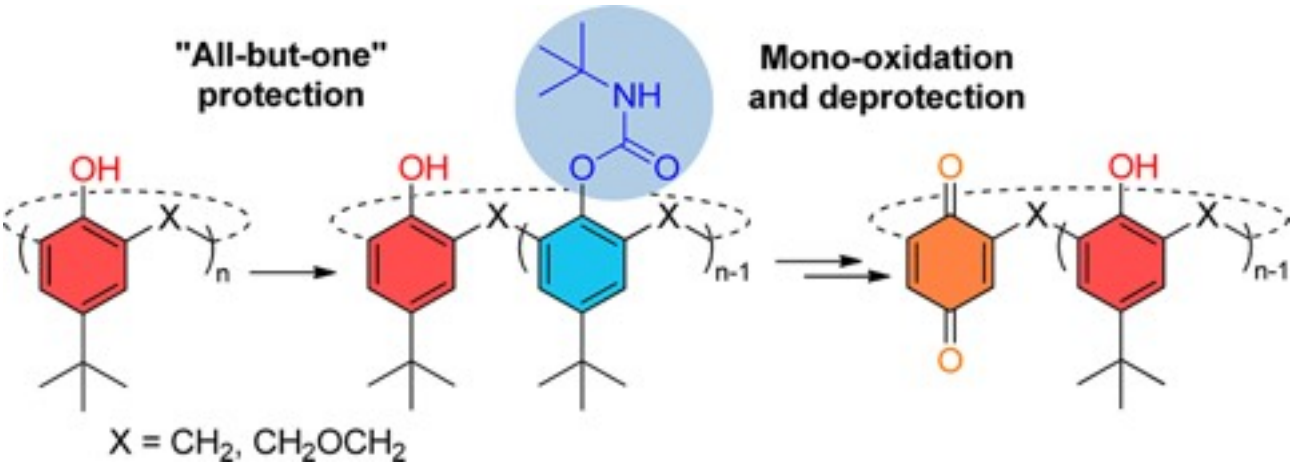
ABSTRACT: The iteroselective “all-but-one” carbamatation methodology has been successfully extended to homooxacalix- arenes and used for the selective and controlled synthesis of homooxacalixarene −monoquinones and calixarene−monoqui- nones. These moquinone derivatives constitute interesting molecular platforms that, until now, were inaccessible through any efficient means.



Calixarenes are extensively exploited in supramolecular platforms. In this regard, we were interested in the chemistry. Their selective modification is often crucial for the controlled introduction of recognition, sensing, chiral, or water-soluble subunits. However, these macrocyclic plat- forms possess multiple identical functional groups which may all react during functionalization reactions. Thus, control of the chemo-, regio-, and stereoselectivity as well as of the iteroselectivity[3] is mandatory.

In this context, we recently described a general, efficient, and rational method for the iteroselective functionalization of calix[4, 5, 6, or 8]arenes.[4] The method consists of reacting the calixarene with tert-butyl isocyanate (t-BuNCO) under basic conditions in an apolar solvent. With this very simple one- step procedure, derivatives bearing N-tert-butylaminocarbonyl (Bac) groups on all but one phenol unit of the starting calixarene are readily obtained in high yield (>90%) (see Figure 1 in the cases of calix[6]arenes 1 and 2). The remarkable iteroselectivity of this so-called “all-but-one” carbamatation methodology was rationalized by an internal proton-assisted mechanism (Figure 1): a single phenolate remains unreacted because no more neighboring phenol group can assist the reaction with t-BuNCO. In addition, the Bac group can be removed in acidic or basic conditions (e.g., excess of $MeSO_3H$ or alkoxide salts, respectively) and can thus be used as a protecting group. This provides general access to monofunctionalized calixarenes through a sequence consisting of all-but-one protection/functionalization/depro- tection.[5]

As part of our continuous interest in the design of macrocyclic receptors,[6] we wanted to see if the all-but-one methodology could be extended to other polyphenolic modification of heteracalixarenes and in particular of

homooxacalixarenes.[8] Although these intriguing compounds have been known for decades, they have been more intensively studied in recent years, notably for the design of efficient molecular receptors.[9] Since our aim was also to emphasize the usefulness of the all-but-one carbamatation, we decided to evaluate this method for the selective introduction of a single p-quinone unit on calixarenes and homooxacalix- arenes. Indeed, due to the binding, redox, and photophysical properties of quinones moieties,[10] calixquinones constitute very attractive compounds that can find a wide range of applications.[11] Despite the potential of calixarene−mono- quinones and homooxacalixarene−monoquinones in supra- molecular chemistry, only the synthesis of calix[4]arene− monoquinones has been described until now.[12]

Herein we describe (i) the extension of the all-but-one carbamatation to homooxacalixarenes and (ii) a general strategy for the selective and controlled introduction of a single p-quinone unit on both calixarenes and homooxacalix- arenes.

First, the reaction conditions that were found as optimal for the all-but-one carbamatation of calixarenes (i.e., t-BuNCO and $Ba(OH)_2 \cdot 8H_2O$ in CH_2Cl_2 at rt) were applied to homooxacalixarenes 3 and 4. To our delight, the desired compounds 3a and 4a, with only one unfunctionalized phenol left, were obtained in high yields after flash chromatography

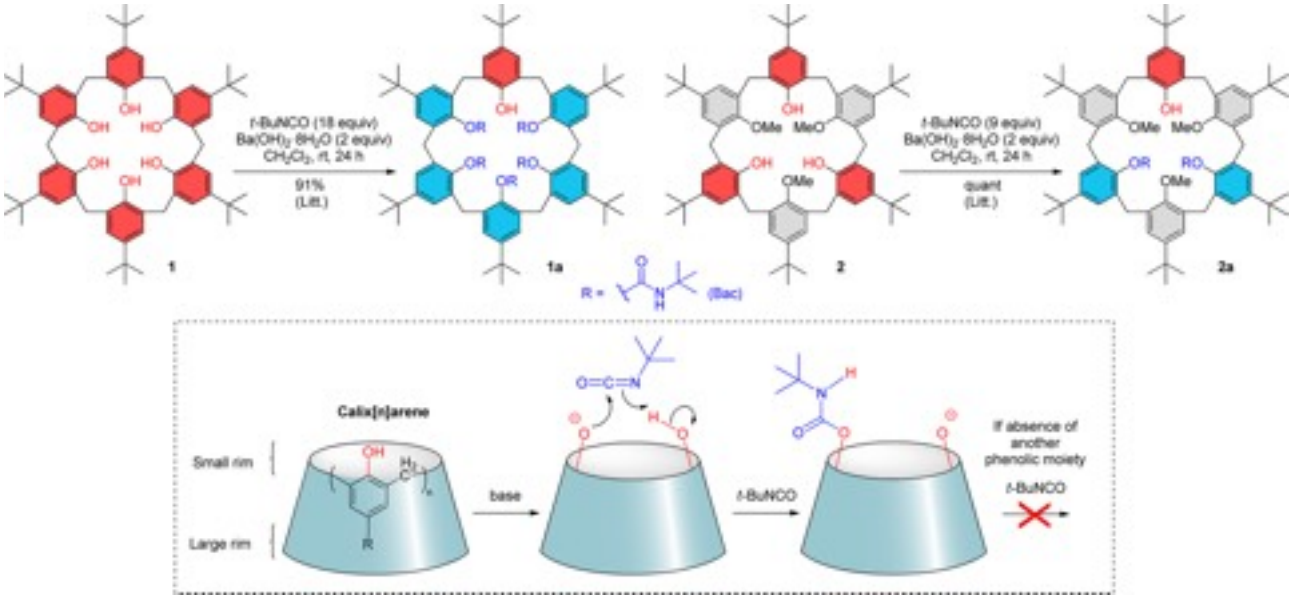


Figure 1. (Top) All-but-one iteroselective carbamatation of calix[6]arenes 1 and 2. (Bottom) Rationale of the iteroselectivity. Bac = N-tert- butylaminocarbonyl.

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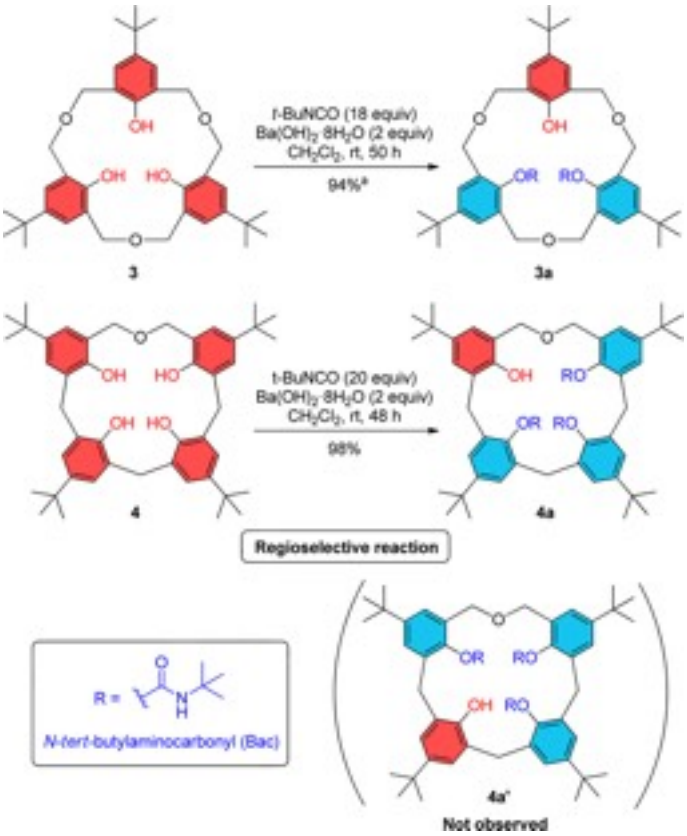
purification (Scheme 1).[13] It is noteworthy that, in both cases, the per-carbamated products were not detected by ESI-MS analysis of the crude reaction mixture, highlighting the remarkable iteroselectivity of the process. Furthermore, as illustrated for 4 in Figure 2, the ^1H NMR spectra recorded before and after purification clearly indicate that the carbamatation yields a single major product. Hence, these first results show that the “all-but-one” iteroselective carbamatation can be efficiently extended from calixarenes to heteracalixarenes such as homooxacalixarenes.

Scheme 1. Extension of the All-but-One Methodology to Homooxacalixarenes 3 and 4[a]



[a]Yield calculated by taking into account the 67% conversion of 3 (63% yield otherwise).

To the best of our knowledge, 4a is the first trifunctionalized dihomooxacalix[4]arene ever reported. This compound was characterized through exhaustive 1D and 2D NMR analyses, and its substitution pattern was deduced from the HMBC spectrum (Figure 2). Indeed, this latter shows a ^{3}J correlation between the axial proton of the $Ar_{OH}-CH_2-O$ methyleneoxy bridge observed at 4.72 ppm and the quaternary carbon bearing the phenolic OH group at 152.6 ppm (correlation labeled “b” in Figure 2), attesting that the remaining phenol moiety is bound to the methyleneoxy bridge. Very interestingly, the other possible regioisomer 4a′ (Scheme 1) was not detected by ^{1}H NMR analysis after purification or in the crude product (Figure 2). Actually, the carbamatation of 4 constitutes the very first example of a regioselective all-but-one carbamatation. In addition to being fully iteroselective with both 3 and 4, as well as fully regioselective with 4, the all-but-one carbamatation also revealed to be atroposelective with both substrates. Indeed, a single conformational stereoisomer was observed, even in the crude reaction mixtures. The ^{1}H NMR pattern of 3a is characteristic of a C_s symmetrical compound, indicating that both carbamated moieties display a syn relationship. In the case of 4a, according to “Mendoza’s single ^{13}C NMR” rule,[14] the ^{13}C chemical shift data of the Ar $-CH_2-$Ar methylene bridges (30−32 ppm) suggest that all the aromatic rings are oriented syn to each other, and this was confirmed by the correlations observed in the ROESY spectrum.[15]

With the partially protected building blocks 1a−4a in hand, we next moved to the synthesis of the corresponding monoquinone derivatives through oxidation of the remaining phenol unit. Since homooxacalixarenes and Bac groups are sensitive to strong acidic media, the conditions usually described

for the oxidation of p-t-Bu-calixarenes into calixquinones (i.e., thallium(III) salts in trifluoroacetic acid)[16] were proscribed. It was shown that PbO_2 under weak acidic conditions was able to convert para-substituted

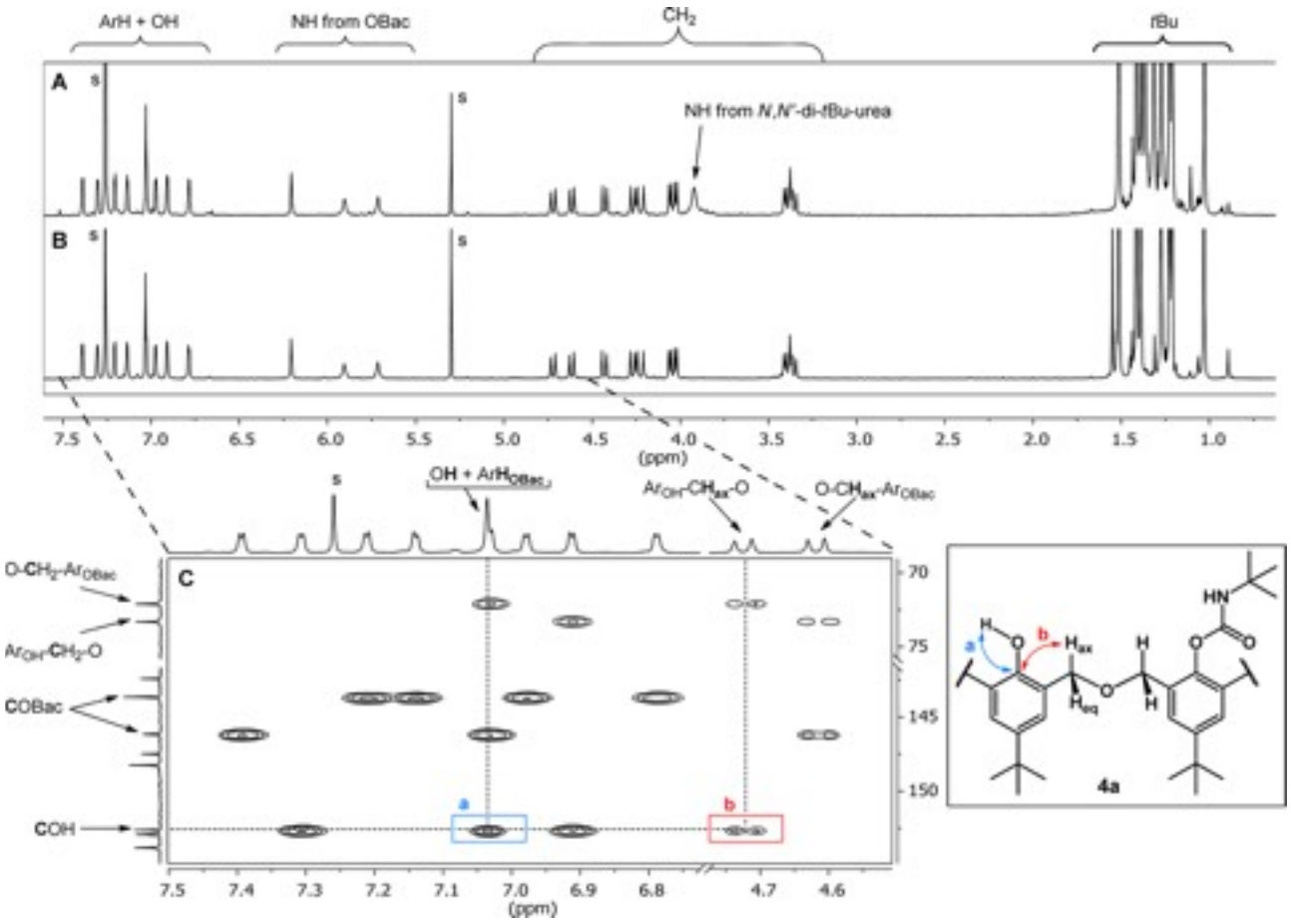


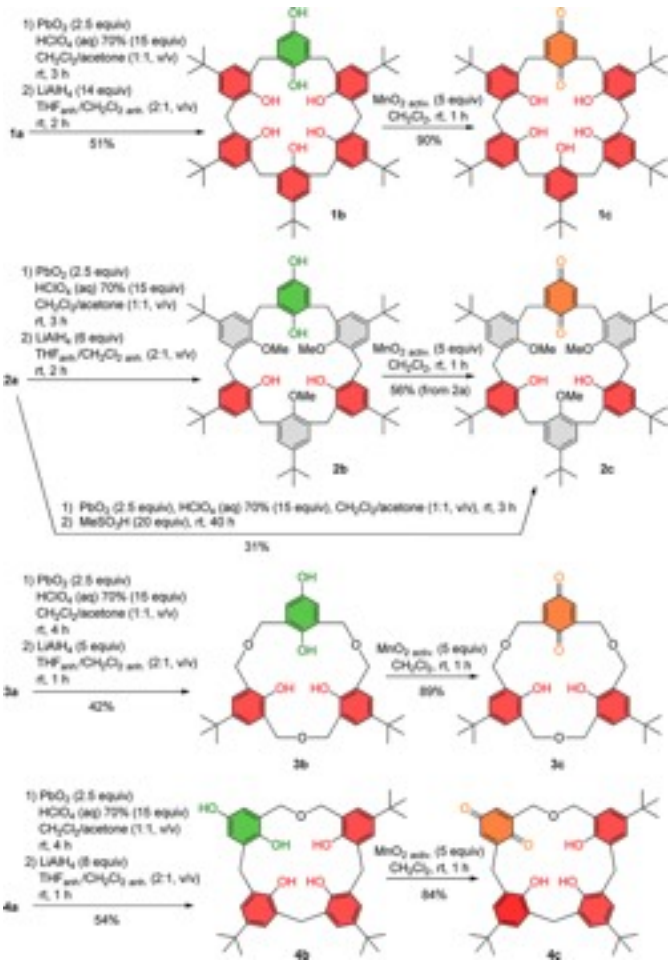
Figure 2. NMR spectra recorded after carbamatation of the dihomooxacalix[4]arene 4 ($CDCl_3$, 298 K, 9.4 T): (A) ^1H spectrum of the reaction mixture after 44 h, (B) ^1H spectrum after purification, (C) regions of the 8 Hz-HMBC spectrum showing the ^2J (a in blue) and ^3J (b in red) ^1H–^{13}C correlations expected for the regioisomer 4a (also see the Supporting Information).

phenols into the corresponding p-benzoquinones.[17] These milder conditions were thus applied to (homooxa)calixarenes 1a−4a, and to our delight, ESI-MS monitoring of the reactions showed the formation of the corresponding (homooxa)calixarene−monoquinones. However, in all cases, TLC and NMR analyses of the crude product indicated the formation of unidentified minor byproducts that were extremely difficult to separate from the main monoquinone product.[18] Therefore, the subsequent cleavage of the Bac groups was achieved on the crude materials. As expected, classical acidic conditions for the removal of the Bac groups (i.e., $MeSO_3H$ in CH_2Cl_2) led to degradation products because of the low stability of the homooxacalixarene skeleton and quinones under these conditions. It was, however, possible to isolate the calixarene−monoquinone 2c but in a low 31% yield from 2a (Scheme 2). Similarly, degradation of all the oxidized intermediates also occurred under basic conditions. Since the reduction of an O-arylcarbamate usually leads to the release of the corresponding phenol,[19] the use of reducing agents (e.g., $Na_2S_2O_5$, $NaBH_4$, BH_3, $LiAlH_4$) was therefore evaluated through careful ESI-MS monitoring. Best results were obtained with $LiAlH_4$, which led to the (homooxa)calixarene−monohydroquinones 1b−4b after de-protection of the carbamated phenols and reduction of the quinone into the corresponding hydroquinone

(Scheme 2). Monohydroquinones 1b, 3b, and 4b underwent very slow air oxidation into the corresponding monoquinones 1c, 3c, and 4c. However, these intermediate hydroquinones were stable enough to be purified through flash chromatography and were thus fully characterized. In contrast, partial oxidation of 2b into calixarene−monoquinone 2c occurred during either the workup or the purification process, preventing its isolation. In the case of 2b, anisole units separate the hydroquinone moiety from the H-bond donor phenol units. The lower stability of this compound might therefore be due to its lower ability to stabilize the hydroquinone moiety through intra- molecular H-bonding interactions. Finally, compounds 1b−4b were treated with activated MnO_2 and a simple filtration on Celite afforded the desired (homooxa)calixarene −monoqui- nones 1c−4c in good yields (Scheme 2).

For comparison's purpose, direct oxidation of calixarenes 1 and 2 with appropriate amounts of PbO_2 was also attempted. In both cases, ESI-MS monitoring of the reactions show the rapid formation of complex mixtures of the starting material and the corresponding multioxidized calixarenes. This result highlights the usefulness of our strategy that consists in using the all-but-one carbamatation as a tool for the selective modification of polyphenolic platforms. It is noteworthy that dihomooxacalix[4]arenes 4a, 4b, and 4c are inherently chiral,[20] and thus their synthesis open interesting perspectives in the field of chiral recognition. Another interesting point is that products 4b and 4c are the first examples of dihomooxacalix[4]arenes selectively modified on one phenolic moiety bound to the methyleneoxymethylene bridge. Moreover, 3c and 4c constitutes the first examples of homooxacalixarenes bearing a quinone moiety.

Scheme 2. Synthesis of the (Homooxa)calixarene−monoquinones 1c−4c from the Corresponding Bac-Protected (Homooxa)calixarenes 1a−4a



In conclusion, we have shown that the all-but-one carbamatation could be extended to homooxacalixarenes and that the reaction is atroposelective and also completely regioselective in the case of the dihomooxacalix[4]arene 4. If this iteroselective protection method is combined with mild oxidation conditions, it gives easy access to (homooxa)- calixarene−monoquinones and (homooxa)calixarene−mono-hydroquinones. These compounds constitute interesting molecular platforms that, until now, were inaccessible through any efficient means. Current work is directed toward studying the host−guest properties of the newly synthesized (homooxa)calixarene−monoquinones as well as other receptors developed from these building blocks.

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taking into account the 67% conversion of 3. Attempts to increase the conversion (i.e., prolonged reaction time, larger excess of t- BuNCO or use of other bases) failed.

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