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Regioselective *O*-Substitution of *C*-Undecylresorcin[4]arene

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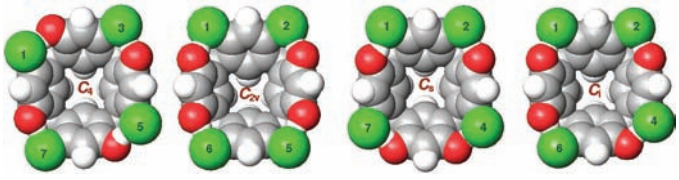
ABSTRACT



Selectively functionalized resorcinarenes were obtained by weak-base-promoted *O*-alkylation of *C*-undecylresorcin[4]arene 1. Tetrasubstituted derivatives with C_4-1,3,5,7, C_{2v}-1,2,5,6, C_s-1,2,4,7, and C_1-1,2,4,6 pattern were obtained in workable yields by using K_2CO_3 as the base in acetone at reflux. The good regioselectivity with respect to the statistical distribution was explained in terms of preferential formation of H-bonded monoanions. Heptaaroylated resorcin[4]arenes were also easily obtained by reaction of 1 with aroyl chlorides in pyridine.

In the past two decades, resorcinarenes[1] have proven to be particularly useful building blocks for the construction of a large variety of supramolecular hosts, which include cavitands,[2] carcerands,[3] and self-assembled capsules.[4] Consequently, their chemical modification has been deeply investigated, mainly concerning exhaustive functionalization,[1] whereas the partial derivatization has remained largely less studied.[5]

Therefore, in sharp contrast with the related calixarene macrocycles,[6] only a very scarce number of regioselective *O*-substitution procedures for resorcinarenes are currently available.[7] The most notable one regards the regioselective direct synthesis of C_{2v} tetra-*O*-sulfonyl or -aroyl derivatives,[8] which have been used for further synthetic elaboration.[9]

An interesting point in this regard is to verify if some of the principles learned from the calixarene chemistry[6] could be usefully transferred to resorcinarenes. Therefore, we decided to investigate the regiochemical outcome of some classical conditions of regioselective *O*-substitution of calixarenes when applied to resorcinarenes.

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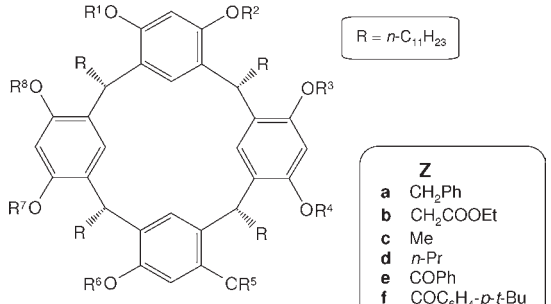
As a first step, we studied the weak-base-promoted *O*-substitution of resorcin[4]arene **1** under the so-called "alternate alkylation" conditions, which are known to afford the 1,3,5,7-tetrasubstitution in the calix[8]arene series.[10] Therefore, we subjected octol **1** to alkylation with an excess of benzyl bromide (10 equiv) in the presence of K_2CO_3 (4 equiv) as the weak base in acetone at reflux. Column chromatography of the crude reaction mixture afforded four tetra-*O*-benzylated derivatives (Table 1, entry 1), namely, **2a** (8%), **3a** (26%), **4a** (9%), and **5a** (23%).[11] This result is particularly interesting because 40 partially substituted derivatives (excluding the enantiomers) could be theoretically obtainable from **1** and, in particular, 12 possible tetrasubstituted regioisomers.[12]



1 $R^{1\text{-}8}$ = H
2a-d $R^{1,3,5,7}$ = Z, $R^{2,4,6,8}$ = H
3a-d $R^{1,2,5,6}$ = Z, $R^{3,4,7,8}$ = H
4a-d $R^{1,2,4,7}$ = Z, $R^{3,5,6,8}$ = H
5a-d $R^{1,2,4,6}$ = Z, $R^{3,5,7,8}$ = H
6e-g $R^{1\text{-}8}$ = Z
7e-g $R^{1\text{-}7}$ = Z, R^{8} = H

This unexpected good regioselectivity with respect to the statistical distribution induced us to extend the above conditions to other alkylating agents, such as ethyl bromoacetate, methyl iodide, and *n*-propyl iodide. As shown in Table 1 (entries 2−4), in all of these instances, the same regiochemical outcome was observed, suggesting a wide applicability for this procedure.[11] The only attention to be paid is in regards to the modulation of reaction time and equivalents of electrophile according to its reactivity or volatility (from 4 to 14 h and from 5 to 50 equiv, respectively, Table 1).

Structure assignment for the above *O*-substituted resorcin[4]arenes relied essentially on spectral analysis. The tetrasubstitution was confirmed by ESI(+) MS spectra, while the assignment of the substitution pattern was based on a careful analysis of ^{1}H and ^{13}C NMR data aided by 2D NMR experiments.[11] The C_4 symmetry of **2a** was straightforwardly proved by the presence in the ^{1}H NMR spectrum of one signal for the bridging methine groups, two singlets for the upper and lower ArH protons, and one resonance for benzylic OCH_2 groups (Figure 1a). In a similar way, the C_{2v} symmetry of 1,2,5,6-tetrasubstituted **3a** was demonstrated by one resonance for the ArCHAr groups and four singlets for the upper and lower ArH protons (Figure 1b).

(11) See Supporting Information for further details.

(12) These 40 partially substituted regioisomers are represented in Chart S3 of Supporting Information.

Table 1. *O*-Substitution Products of Resorcin[4]arene (**1**) in Acetone at Reflux

entry	electrophile (equiv)	base (equiv)	time (h)	isolated compd (yield %)[a]
1	$PhCH_2Br$ (10)	K_2CO_3 (4.0)	14	**2a** (8), **3a** (26), **4a** (9), **5a** (23)
2	$BrCH_2COOEt$ (5)	K_2CO_3 (4.0)	4	**2b** (10), **3b** (28), **4b** (12),[b] **5b** (32)[b]
3	MeI (50)	K_2CO_3 (4.0)	5	**2c** (9), **3c** (25), **4c** (11),[b] **5c** (30)[b]
4	*n*-PrI (10)	K_2CO_3 (4.0)	14	**2d** (7), **3d** (21), **4d** (9),[b] **5d** (27)[b]

[a] The yields refer to procedures optimized by changing reaction times and equivs of electrophile. [b] In this instance, compounds **4** and **5** were obtained as a mixture only resolvable by HPLC.

The C_s 1,2,4,7-tetrasubstitution pattern of **4a** was proven by the presence of two sets of three ArH resonances in a 1:2:1 ratio (Figure 1c) that excluded the C_s 1,2,3,4- and 1,4,6,7-tetrasubstitution patterns. The remaining C_s 1,2,3,8-tetrasubstitution was excluded on the basis of clear ROESY correlations between OH and OCH_2 resonances, only compatible with the 1,2,4,7 pattern. An alternative way to assign this substitution pattern can be based on the different chemical shift of "isolated" (6.78−7.10 ppm) or "H-bonded" (8.02−9.20 ppm) OH groups.[13,14] In fact, **4a** shows only isolated OH groups resonating in the 6.85−6.91 ppm range and only compatible with the 1,2,4,7-tetrasubstitution pattern.

The unsymmetrical 1,2,4,6-substitution pattern of **5a**, evidenced by eight ArH singlets, was also assigned by considering the presence of four isolated OH signals (7.08, 6.98, 6.86, and 6.82 ppm) only compatible with the 1,2,4,6-tetrasubstitution (Figure 1d). A ROESY spectrum was in full accordance with this conclusion.

(13) This method has been successfully applied in the calixarene series. See, refs 10a and 10c and the following: (a) Kraft, D.; Arnecke, R.; Böhmer, V.; Vogt, W. *Tetrahedron* **1993**, *49*, 6019. (b) Stewart, D. R.; Krawiec, M.; Kashyap, R. P.; Watson, W. H.; Gutsche, C. D. *J. Am. Chem. Soc.* **1995**, *117*, 586. (c) Cunsolo, F.; Consoli, G. M. L.; Piattelli, M.; Neri, P. *J. Org. Chem.* **1998**, *63*, 6852. (d) Gaeta, C.; Gregoli, L.; Neri, P. *Tetrahedron Lett.* **2002**, *43*, 9521. (e) Martino, M.; Gaeta, C.; Neri, P. *Tetrahedron Lett.* **2004**, *45*, 3387. (f) Li, H.; Zhan, J. *J. Incl. Phenom. Macrocycl. Chem.* **2008**, *60*, 379.

(14) Typical chemical shift values of isolated OH groups in resorcinarenes are those of 1,3,5,7 **2a** and 1,2,5,6 **3a**. For analogous values of H-bonded OHs, see: Cram, D. J.; Tunstad, L. M.; Knobler, C. B. *J. Org. Chem.* **1992**, *57*, 528.

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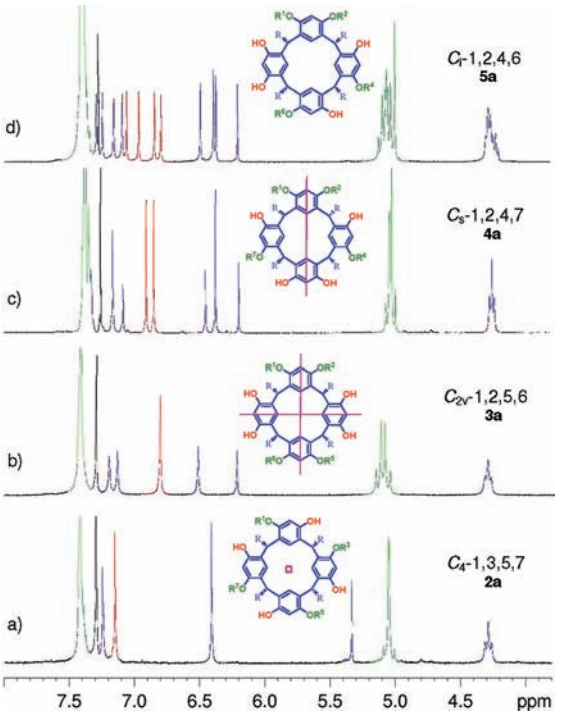
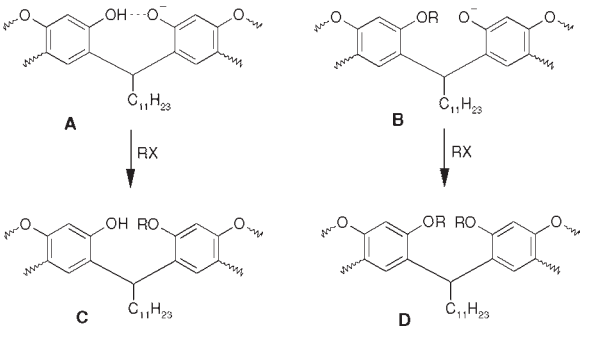


Figure 1. Low-field region of ^{1}H NMR spectra of compounds **2a**, **3a**, **4a**, and **5a**. The signals relative to different groups were colored in accordance with the given structure.

The C_s 1,2,4,7-tetrasubstitution pattern of **4c**,**d** and the C_i 1,2,4,6 pattern of **5c**,**d** were confirmed by chemical correlation with the corresponding tetrabenzylated derivatives **4a** and **5a**, respectively. In fact, upon methylation or propylation of these latter, followed by debenzylation via hydrogenolysis, compounds identical in all respects to **4c**,**d** and **5c**,**d** were obtained, thus confirming their substitution pattern.[11]

The above observed regioselectivity can be easily explained in terms of preferential formation of H-bonded monoanions previously used to explain the outcome of the weak-base-promoted *O*-substitution in the entire series of calix[*n*]arenes.[10,15]

Scheme 1. Possible Resorcinarene Monoanions and Their Alkylation Products



In fact, in this instance, two possible monoanions **A** and **B** (Scheme 1) could be formed in the presence of the weak base in the course of the reaction. Obviously, the H-bonded stabilized monoanion **A** should be formed preferentially, leading to nonproximal substitution of type **C**, whereas the proximal one of type **D** should be disfavored (Scheme 1).

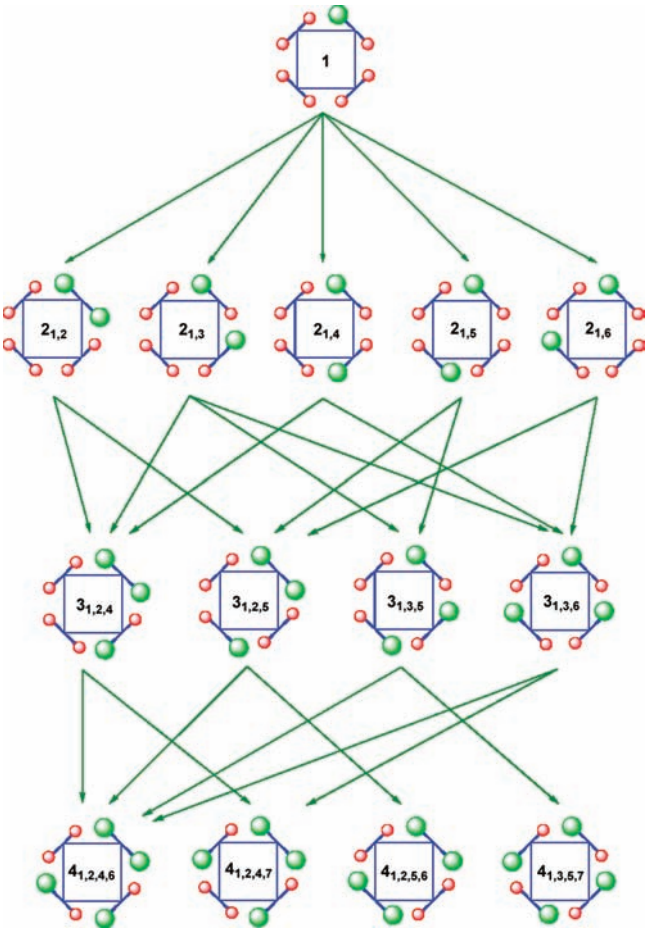


Figure 2. Plausible pathways for the weak-base-promoted tetra-*O*-alkylation of resorcin[4]arene **1**.

Therefore, on the basis of this assumption, all favored products should be derived by any combination of nonproximal substitution **C**. As it is easy to verify, all those possible combinations are represented by the four tetrasubstitution patterns here obtained, namely, the 1,3,5,7, 1,2,5,6, 1,2,4,7, and 1,2,4,6 ones, thus lending support to the above explanation. On this basis, a plausible pathway of the weak-base-promoted *O*-alkylation can be drawn, in which monoanions **B** are excluded that lead to the observed tetrasubstitution patterns (Figure 2).

As a second step, we decided to investigate the aroylation of resorcin[4]arene **1** with aroyl chlorides in pyridine. In fact, this procedure can easily afford hepta- or octaesters of *p*-*tert*-butylcalix[8]arene in good yields by simply adjusting the molar ratio of the reactants.[16]

As expected, the reaction of **1** with a large excess of aroyl chlorides (20 equiv) easily afforded the corresponding octaaroylates **6e**–**g** in good yields (Table 2, entries 1–3). Interestingly, the use of 10 equiv of acylating agent, also in these instances, allowed the isolation of satisfying yields (44–55%) of heptaaroylates **7e**–**g** (Table 2, entries 4–6).

Table 2. *O*-Substitution Products of Resorcin[4]arene (**1**) in Pyridine at Room Temperature

entry	electrophile (equiv)	time	isolated compd (yield %)
1	PhCOCl (20)	2 h	**6e** (99)
2	*p*-*tert*-Bu-C_6H_4COCl (20)	2 h	**6f** (98)
3	*p*-Cl-C_6H_4COCl (20)	2 h	**6g** (87)
4	PhCOCl (10)	15 min	**6e** (40), **7e** (55)
5	*p*-*tert*-Bu-C_6H_4COCl (10)	1 h	**6f** (37), **7f** (44)
6	*p*-Cl-C_6H_4COCl (10)	45 min	**6g** (35), **7g** (50)

In analogy, with the corresponding calix[4]arene tribenzoates,[17] calix[5]arene tetrabenzoate,[18] calix[6]arene pentabenzoate,[19] and calix[8]arene heptabenzoates,[16] which were obtained under very similar conditions, these heptaaroylates **7e**–**g** can be considered as "protected" resorcinarenes for the synthesis of monosubstituted derivatives.[20]

In all these instances, it is conceivable that the last step of exhaustive acylation is significantly slower than the previous one for statistical reasons and because of the increased overcrowding.

It is interesting to point out that resorcinarenes **2a**–**c**, **4a**–**c**, and **7e**–**g** are inherently chiral compounds.[21] In some instances, their racemic nature was proved by the doubling of some resonances in their ^{1}H NMR spectra upon addition of Pirkle's reagent and by resolution via enantioselective HPLC on Chiralpak ADH stationary phase (Figure 3).[11]

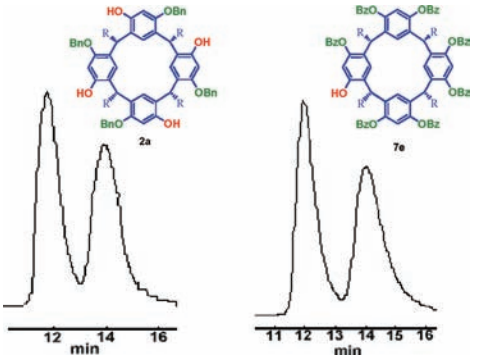


Figure 3. HPLC enantioresolution of compounds **2a** and **7e** (left and right, respectively) at 98/2 (v/v) of *n*-hexane/2-propanol. Flow rate = 0.6 and 0.8 mL/min, respectively.

In conclusion, we have reported here two synthetic procedures for the preparation of partially *O*-substituted resorcin[4]arenes that in some instances possess an unprecedented substitution pattern. The partially benzylated or benzoylated derivatives can be considered as protected resorcinarenes to obtain hardly accessible compounds. The reported results represent an interesting example of application of previously learned principles that leads to a deeper understanding of the chemical behavior of the enlarged calixarene/resorcinarene family.

Acknowledgment. The authors thank Dr. Patrizia Iannece (Dipartimento di Chimica e Biologia, Università di Salerno) for elemental analyses.

Supporting Information Available. Synthetic details, 1D and 2D NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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