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Photoisomerizable azobenzene-containing oxacalixarenes

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ABSTRACT

The first examples of photo-responsive azobenzene-containing oxacalixarenes have been synthesized via a 3+1 macrocyclization approach. Introduction of the photoresponsive unit was achieved by using 4-phenylazoresorcinol or (*E*)-4-(4'-nitrophenylazo)resorcinol as the nucleophilic component in the macrocyclization reaction. These novel macrocycles have been characterized by means of 1D and 2D NMR spectroscopy and DFT calculations (B3LYP/6-31G(d)). According to thermal and photoisomerization studies, tetranitro-oxacalix[4]arenes are less prone to $E \rightarrow Z$ isomerization than oxacalix[2]arene[2]triazines and, within the two series, *p*-nitrophenylazo derivatives are more unwilling to isomerize than their phenylazo analogues.

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The synthesis of the earliest crown ethers¹ and the discovery of their ability to act as molecular receptors have been the prime movers in the development of host-guest chemistry and, from there, of the broader multidisciplinary field of supramolecular chemistry. Since then, a wide variety of different macrocyclic compounds—cyclodextrins² and calixarenes,³ to name the most relevant examples—have been shown to possess analogous or even better molecular recognition properties. Others such as heteraca-lixarenes⁴ (and in particular aza- and oxacalixarenes), although extremely appealing for the purpose of molecular recognition, have not yet been widely investigated, primarily because of the lack of convenient procedures for their synthesis and/or further derivatization.

Oxacalixarenes, for instance, have only recently started to gain increasing attention, despite the fact that their discovery goes back to 1966.⁵ Differently from the parent calixarenes, these oxa[1₄]metacyclophanes are commonly prepared by S_NAr one-pot reaction of aromatic diols with electron deficient dihaloaromatic (or heteroaromatic) compounds.^{4a-d} This method provides access to a large number of different oxacalix[4]arenes in moderate to very good yields, by making use of a variety of easily available nucleophilic and electrophilic components.⁶ However, no matter how efficient this synthetic approach is, it does not yield macrocycles with sequences of (hetero)aromatic units different from the simplest ABAB one.

Wang et al.⁷ have lately reported a new and convenient synthetic route to oxacalix[2]arene[2]triazines, reliant on a 3+1 fragment coupling two-step synthesis, which takes advantage of the relative reactivity of the halogen substituents present on the 2,4,6-trichloro-1,3,5-triazine ring. Such an approach, which can easily be applied to analogous systems,⁸ has paved the way for the preparation of oxacalix[*n*]arenes composed of three or more different (hetero)aromatic units.⁹

Given the potential of the above-mentioned method, the synthesis of azobenzene-containing oxacalixarenes was considered on the basis of the key role played by photoresponsive moieties in the development of powerful molecular receptors.¹⁰ Azobenzene moieties—because of their tendency to undergo reversible E/Z photoisomerization¹¹—are well known to induce conformational modification on the macrocyclic framework they are attached to and, as a result, may prompt selective capture and/or controlled release of a target substrate.¹⁰ Herein, as a follow-up of our recent studies on tetraureido-¹² and enantiomerically pure BINOL-containing oxacalix[4]arenes,¹³ we wish to report on the synthesis of the first oxacalixarenes bearing azobenzene groups along with a preliminary study on their light-induced and thermal E/Z isomerization.

Oxacalix[4]arenes (*E*)-**1a,b** and oxacalix[2]arene[2]triazines (*E*)-**2a,b** were prepared by 3+1 fragment condensation starting from the known precursors $\mathbf{3}^{14}$ and $\mathbf{4}^{7}$ respectively. These triaryl compounds were in turn reacted with either (*E*)-4-phenylazoresorcinol (Sudan Orange G) or (*E*)-4-(4'-nitrophenylazo)resorcinol according to Scheme 1. Difluoro derivative **3** was treated with equimolar

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Scheme 1. Synthesis of oxacalixarenes (E)-1a,b and (E)-2a,b.

amounts of the relevant azo dye in MeCN (60 °C) in the presence of Et₃N to give oxacalixarenes (*E*)-**1a** and (*E*)-**1b** in a 61% and a 91% yield, respectively. The reaction with tetrachloro intermediate **4**, on the other hand, was carried out in acetone at room temperature using *i*-Pr₂NEt as the base. Macrocyclizations in this case produced, compounds (*E*)-**2a** and (*E*)-**2b** in an 17%¹⁴ and a 87% isolated yield.

Oxacalixarenes (*E*)-**1a,b** and (*E*)-**2a,b** were characterized by ¹H and ¹³C NMR and UV-vis spectroscopy. ¹H NMR spectra of compounds (*E*)-**1a,b** suggest that these compounds adopt in solution a 1,3-alternate saddle-shaped conformation. This type of structural arrangement is consistent with the significant highfield shift of the resonances assigned¹⁵ to the intra-annular hydrogen atoms of the

dinitroaromatic units (δ = 6.05–6.21 ppm, Fig. 1) which, in analogous systems,^{4a-c,12} has been attributed to the anisotropic shielding induced by the flanking resorcinol rings. In addition, in both macrocycle pairs, the peaks for the hydrogen atom of the unsubstituted resorcinol unit are shifted toward higher fields with respect to the same signals of the relevant precursors ($\Delta \delta$ = 0.09–0.17 and 0.29–0.43 ppm for (*E*)–**1a,b** and (*E*)–**2a,b**, respectively), most probably as the result of a mutual shielding between the resorcinol mojeties.

Additional evidence in favor of a 1,3-alternate saddle-shaped conformation of derivatives (E)-1a,b and (E)-2a,b was also collected by carrying out molecular modeling calculations¹⁶ at the density functional level of theory (B3LYP/6-31G(d),¹⁷ see Table S1 and Figs. S5-S8 in the Supplementary data). This preferential conformation arrangement, which has very often been observed in the solid state structure of related oxacalix[4](hetero)arenes.^{4a-c,18,19} derives from the tendency to ensure conjugation between the bridging oxygen atoms and the electron-poor nitroaromatic rings.4a-c

As far as the absorption spectra are concerned, oxacalixarenes (*E*)-**1a,b** and (*E*)-**2a,b** consistently show a weak band in the visible and an intense one in the near UV region, typical of the azobenzene moiety (Fig. 2).^{11a,20} In addition, derivatives (*E*)-**1a,b** display a high-intensity band (centered at 267 nm), likely due to a $\pi \rightarrow \pi^*$ transition involving the dinitroaryl moieties of the oxacalix[4]arene framework.²¹ The spectral differences between the pairs of pheny-lazo and *p*-nitrophenylazo-substituted macrocycles (**1a/2a** and **1b/2b**, respectively) can be attributed to the presence of the nitro-substituent on the azobenzene subunit. Such an electron-withdrawing group induces a lower energy shift ($\Delta \lambda_{max}$ ca. 10–14 nm) on the S₂ $\pi \rightarrow \pi *$ transitions of the latter pair, perturbing at the same time their S₁ $n \rightarrow \pi *$ transitions (broadening of the bands in the 400–550 nm region).

With a view to subsequent use of these oxacalixarene derivatives as potential photoresponsive molecular receptors, preliminary isomerization experiments (λ = 365 nm 16 h, rt, CDCl₃) were carried out. Analysis of the ¹H NMR spectra of the irradiated samples (Fig. S13) revealed that all compounds undergo photoisomerization, producing mixtures of the *E*- and *Z*-isomers—albeit with



Figure 1. ¹H NMR spectra (500 MHz, CDCl₃, 25 °C, 5 mM) of oxacalix[4]arenes (E)-1a,b and oxacalix[2]arene[2]triazines (E)-2a,b.



Figure 2. Absorption spectra (5.5×10^{-5} M, CH₂Cl₂, $25 \circ$ C) of **1a,b** and **2a,b** in the *E*-form (solid line) and in the photo-stationary state (dashed line) reached after 1 h irradiation at λ = 334 nm. Insets show the fatigue-cycle plots.

very different ratios—**2a** being the most prone to isomerization and **1b** the most resistant (see below, Table 1). Spectra of the *Z*-isomers differ significantly from those of the parent *E*-isomers as a result of the shielding effect produced by the isomerized exocyclic ring. Furthermore, molecular modeling (Fig. S9–S12) suggests that the change in the configuration of the N=N double bond affects the conformation of the macrocycle, determining slight modifications of the aryl–aryl interplanar angles (Table S1).

The dependence of the azobenzene photoisomerization process $(E \rightleftharpoons Z)$ on the nature of the macrocyclic frameworks was subsequently investigated via UV–vis spectroscopy, by selectively irradiating (λ = 334 and 432 nm) CH₂Cl₂ solutions of **1a,b** and **2a,b**. (*E*)-Diphenyldiazene was chosen as a reference compound for these experiments.²² In all instances, the absorption spectra of the *E*-and *Z*-isomers were found to partially overlap (Fig. 2) and, as a consequence, upon irradiation at λ = 334 nm a stationary state was reached.²³ The changes in shape and energy of the absorption bands are similar to those observed for the reference (*E*)-diphenyl-diazene (Fig. S14). At equilibrium, the S₁ band of each macrocycle undergoes a small hyperchromic effect whereas the S₂ one experiences a hypsochromic shift and a substantial hypochromic effect.

Irradiation at λ = 432 nm induces the quantitative reverse isomerization to the *E*-isomer. The photoequilibrium conditions can repeatedly be reached in a cyclic manner with no evidence of product degradation (see insets in Fig. 2).

Data in Table 1 also indicate that the $E \rightarrow Z$ photoisomerization process becomes less efficient when the *p*-nitro-substituent is

Table 1	
Selected parameters for the isomerization of 1a,b and 2a,b	

	${\varPhi_{E o Z}}^{a}$	$(E/Z_{ratio})^{b}$	$k_{Z \to E}/s^{-1c}$
1a	0.13	(44:56)	$4.0 imes10^{-4}$
1b	0.10	(71:29)	$6.2 imes10^{-4}$
2a	0.15	(8:92)	$1.3 imes 10^{-5}$
2b	0.12	(51:49)	2.5×10^{-5}

^a Irradiation at 334 nm.

^b Obtained by direct integration of relevant peaks present in the ¹H NMR spectra (Fig. S13).

^c Measured at 25 °C.

present on the azobenzene moiety. Accordingly, the quantum yields decrease from 0.13 to 0.10 for **1a** and **1b**, respectively, and from 0.15 to 0.12 for **2a** and **2b**. Both composition of the photostationary states and the quantum yield values indicate that the *p*-nitro substituent in **1b** and **2b** significantly lowers the efficiency of the photoisomerization process. In addition, in the case of **1b** isomerization is further inhibited by the presence of the four nitro groups on the oxacalixarene macrocycle.

In line with the known process of thermal reverse isomerization of (*Z*)-azobenzene derivatives²⁴ to the corresponding *E*-isomers in the dark, oxacalixarenes (*Z*)-**1a,b** and (*Z*)-**2a,b** (CH_2Cl_2 ,²⁵ 25 °C) were found to revert back to their *E*-isomers with first-order kinetics (Fig. 3).

Close inspection of the first-order rate constants $(k_{Z\rightarrow E})$ reported in Table 1 confirms that the *p*-nitro group also plays a significant role in the reverse isomerization process, by way of stabilizing more efficiently the *E*- rather than the *Z*-isomers. As a result, *p*nitrophenylazo substituted oxacalixarenes **1b** and **2b** display higher $k_{Z\rightarrow E}$ values than the corresponding phenylazo derivatives **1a**



Figure 3. Absorption variations at 340 nm for the thermal $Z \rightarrow E$ reactions in the dark at 25 °C in CH₂Cl₂.

and **2a** $(6.2 \times 10^{-4} \text{ and } 2.5 \times 10^{-5} \text{ s}^{-1} \text{ vs } 4.0 \times 10^{-4} \text{ and } 1.3 \times 10^{-5} \text{ s}^{-1}$, respectively). Similar rate constant comparison between oxacalix[4]arenes **1a,b** and oxacalix[2]arene[2]triazine **2a,b** reveals that the former pair undergoes thermal $Z \rightarrow E$ isomerization faster than the latter one. According to this cross-comparison, the nature of the oxacalixarene framework affects the excited states involved in the thermal isomerization process of the azobenzene moieties, with the dinitroaryl rings—more than the chlorotriazine ones—exerting a stabilizing effect on the *E*-isomers. This observation is in agreement with the results obtained from the photoisomerization experiments.

In conclusion, we have synthesized the first family of azobenzene-containing photoisomerizable oxacalixarenes and investigated their photoinduced and thermal E/Z isomerization. Additional studies aiming to elucidate the molecular recognition properties of these and other structurally-related oxacalixarenes, along with in-depth investigations on their photoswitching behavior, are currently in progress.

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Supplementary data

Supplementary data (general experimental methods, synthetic procedures, COSY NMR spectra and calculated structures for oxacalixarenes **1a,b** and **2a,b**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.11.114.

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- 22. The tetranitro-oxacalix[4]arene framework of compounds 1a,b does not significantly absorb above 320 nm, and therefore there is no overlap with the relevant bands of the azobenzene moiety.
- 23. The *E*/*Z* concentration ratios depend on the molar absorption coefficients of the two isomers at the excitation wavelength employed, as well as on the quantum yields of the forward and reverse reactions.
- 24. Thermal $Z \rightarrow E$ isomerization of diphenyldiazene is a first-order process that proceeds with an activation energy value close to 24 kcal mol⁻¹ (Ciminelli, C.; Granucci, G.; Persico, M. *Chem.–Eur. J.* **2004**, *10*, 2327–2341).
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