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Photoresponsive upper-rim azobenzene substituted calix[4]resorcinarenes

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Abstract—Photoswitchable calix[4]resorcinarenes with different numbers of azo groups in the upper rim were synthesised by the reaction of bromomethylcavitand with 4-aminoazobenzene. UV–vis, ^{1}H and ^{13}C NMR, MALDI TOF-MS spectral data have been used to elucidate the structures of compounds.

Special types of calix[4]resorcinarenes in cone conformation develop artificial ion channel activity after incorporation into a lipid bilayer and show one conductivity state under normal conditions.[1–4] The integration of photochromic moieties[5] into these types of calix[4]resorcinarenes is attracting interest in order to obtain gated non-peptidic ion channels which can be reversibly switched between open and close positions using light irradiation.

Here we report on the preparation of upper-rim substituted calix[4]resorcinarenes with different numbers of azobenzene groups and on the results of their photoresponsive behaviour under irradiation process in single and multiple azobenzene substituted systems. Such photochromic systems with azo groups can exist in two forms, (*Z*) and (*E*) isomers. Due to photoisomerisation, they have the potential to be used in light-triggered switches, ion-channel-based biosensors and in photomodulated devices.

The intermediate tetrakis(bromomethyl)-cavitand **1** (Fig. 1) was obtained via three steps according to known procedures.[6–9]

Tetrakis(*p*-phenylazophenylaminomethyl)-cavitand **5** (Fig. 1) was synthesised by reacting tetrakis(bromomethyl)-cavitand **1** (Fig. 1) with an excess of 4-aminoazobenzene in the presence of anhydrous sodium carbonate.[†]

[†] General procedure for the synthesis of tetrakis(*p*-phenylazo-phenylaminomethyl)-cavitand **5**[17] from tetrakis(bromomethyl)-cavitand **1** and 4-aminoazobenzene: 0.6 mmol tetrakis(bromomethyl)-cavitand **1** were weighed into a 100 mL three-necked round bottom flask connected with a 50 mL dropping funnel. 30 mL dry DMF and 6 mmol anhydrous sodium carbonate were added and the mixture was stirred at room temperature. During stirring, 3 mmol 4-aminoazobenzene dissolved in 30 mL dry DMF were added dropwise to the mixture over a period of 2 h. After connecting an argon balloon, the mixture was heated to 45 °C and kept under vigorous stirring 5 days. Then, the solvent was removed under high vacuum by Kugel–Rohr distillation and then we made an extraction of the watery solution with a separation funnel from methylene chloride–water (1:1). The crude product was purified by column chromatography (SiO_2, pentane–dichlor methane (1:1) to afford the tetrakis-(*p*-phenylazophenylaminomethyl-cavitand **5**. Besides the tetrakis-(*p*-phenylazophenylaminomethyl)-cavitand **5** we isolated, by column chromatography, 23-methyl-tris(5,11,17-*p*-phenylazophenyl aminomethyl)-cavitand **6**, 11,23-dimethyl-bis(5,17-*p*-phenylazophenyl aminomethyl)-cavitand **7** and 11,17,23-trimethyl-(5-*p*-phenylazophenyl aminomethyl)-cavitand **8**. This is a result of using the intermediate tetrakis(bromomethyl)-cavitand **1** as a mixture [tetrakis(bromomethyl)-cavitand **1**, tris(bromomethyl)-cavitand **2**, bis(bromomethyl)-cavitand **3** and bromomethyl-cavitand **4**] in the reaction with 4-aminoazobenzene. The mixture was used without purification, due to instability of the products on different column materials (e.g., silica and aluminium oxide).

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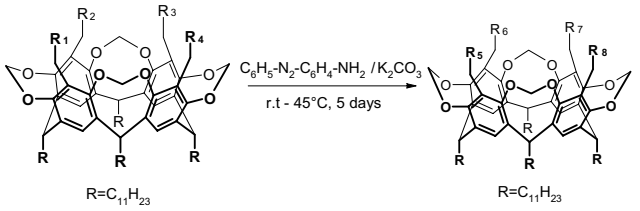

1: $R_1=R_2=R_3=R_4=Br$
2: $R_1=R_2=R_3=Br$, $R_4=H$
3: $R_1=R_3=Br$, $R_2=R_4=H$
4: $R_1=Br$, $R_2=R_3=R_4=H$

5: $R_5=R_6=R_7=R_8=$ (NH-C_6H_4-N=N-C_6H_5)
6: $R_5=R_6=R_7=$ (NH-C_6H_4-N=N-C_6H_5), $R_8=H$
7: $R_5=R_7=$ (NH-C_6H_4-N=N-C_6H_5), $R_6=R_8=H$
8: $R_5=$ (NH-C_6H_4-N=N-C_6H_5), $R_6=R_7=R_8=H$

Figure 1. Synthesis of upper-rim substituted calix[4]resorcinarenes.

Geometrical isomerisation of the azo-functionality by photoirradiation induces large structural changes.

All the irradiation experiments were carried out using a 100 W high-pressure mercury lamp.The optical property of *cis–trans* isomers was changed in acetone solution, at room temperature. The *E–Z* photoisomerisation was monitored using a Perkin–Elmer spectrometer model Lambda 19.

The changes in the absorption spectra of 11,17,23-trimethyl-(5-*p*-phenylazophenylaminomethyl)-cavitand **8** under UV–vis irradiation[10–13] are presented in Figure 2.

In case of 11,17,23-trimethyl-(5-*p*-phenylazophenyl aminomethyl)-cavitand **8** in acetone solution (Fig. 2), the two isomers exhibit well-separated absorption bands in the UV–vis range. Both states were interconverted photochemically using a filter 295 nm < λ < 400 nm for the *E–Z* transformation (5 min) (curve 2 in Fig. 2) and a filter λ > 475 nm for the back reaction (10 min) (curve 3 in Fig. 2). For 11,17,23-trimethyl-(5-*p*-phenylazophenylaminomethyl)-cavitand **8**, two isosbestic points were observed in the absorption spectra at λ = 346 nm and at λ = 454 nm. The fact that the peak at 380 nm for curve 3 exceeds that for curve 1 indicates that both conformers exist in thermal equilibrium.

The absorption spectra of 11,23-dimethyl-bis(5,17-*p*-phenylazophenylaminomethyl)-cavitand **7** (Fig. 3) shows

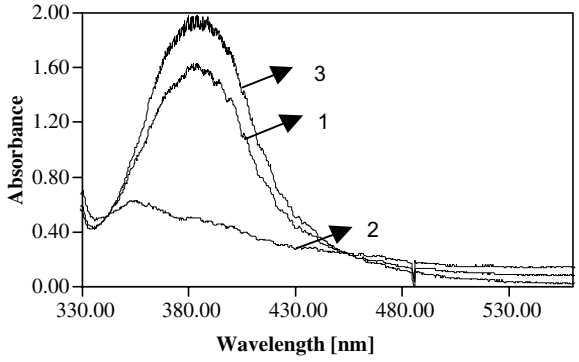

Figure 2. *E,Z*-Isomerisation of 11,17,23-trimethyl-(5-*p*-phenylazophenylaminomethyl)-cavitand **8**. Curve 1: before irradiation, curve 2: after 5 min irradiation (filter 295 nm < λ < 400 nm), curve 3: after 10 min irradiation (filter λ > 475).

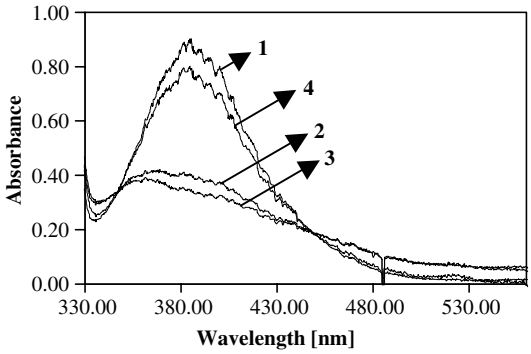

Figure 3. *E,Z*-Isomerisation of 11,23-dimethyl-bis(5,17-*p*-phenylazophenylaminomethyl)-cavitand **7**. Curve 1: before irradiation, curve 2: after 5 min irradiation (filter 295 nm < λ < 400 nm), curve 3: after 6 min irradiation (filter 295 nm < λ < 400 nm), curve 4: after 10 min irradiation (filter λ > 475 nm).

a weak band in the visible range for the *ZZ* isomer about 530 nm and an intense band in UV range for the *EE* isomer at 385 nm.

Curve 1 in Figure 3 represents the thermodynamically favoured *EE* conformation. Upon irradiation with UV light (filter 295 nm < λ < 400 nm) the azobenzene moieties were converted to the *Z*-form (curves 2 and 3 in Fig. 3). The observation of two isosbestic points at 348 and 450 nm suggests that the two azobenzene moieties can move independently with respect to the isomerisation. This also pertains to the back reaction induced by irradiating with visible light (filter λ > 475 nm).

During the photoirradiation process of tetrakis(*p*-phenylazophenylaminomethyl)-cavitand **5**, we have observed intermediate states of *ZZZZ–EEEE* interconversions, (cf. Ref. 14). These can be *ZZZE*, *ZZEE*, *ZEEE*, *ZEZE* forms in case of tetrakis(*p*-phenylazo-phenylaminomethyl)-cavitand **5** which could not be discriminated. During the *EEEE–ZZZZ* transformations we get a light scattering effect due to molecular association formation of the *trans* form of tetrakis(*p*-phenylazophenylaminomethyl)-cavitand **5**. The scattering effect also prohibited the clear-cut observation of isosbestic points.

Since the azobenzene groups of calix[4]resorcinarenes can easily change their configuration between *trans* and *cis* via light excitation, this system is expected to be a viable candidate for light-driven molecular switches.

The applications of these compounds for light-gated artificial ion channels controlled by photoisomerisation and the further investigation to optimise the switch parameters are in progress. The switch will work at room temperature due to the high thermal stability of both the *trans* and the *cis* configurations of azobenzene molecules. Such photoisomerisable azobenzene groups used as photogates (block or let the ions through the ion channel using different wavelengths for irradiation) were successfully tested as molecular photoswitch on natural ion channels (modified Shaker channels[15] and

modified Gramicidin A channels[16]), but not yet on non-peptidic ion channels.

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17. Spectroscopic data of compounds: Tetrakis(*p*-phenylazophenylaminomethyl)-cavitand **5**: ^{1}H NMR (500 MHz, $CDCl_3$, rt): δ (ppm) = 0.86 (t, 12H, CH_3, J = 6.74 Hz), 1.21 (m, 64H, CH_2CH_2), 1.45 (s, 8H, CH_2CH_3), 2.21 (m, 8H, CH_2CH_2CH), 4.16 (d, 8H, CH_2NH), 4.29 (br s, 4H, NH), 4.35 (d, 4H, OCH_2O, J = 6.87 Hz), 4.76 (t, 4H, $CHCH_2$, J = 8.04), 5.96 (d, 4H, OCH_2O, J = 6.81 Hz), 6.76 (d, 8H, Ar*H*, J = 8.68), 7.14 (s, 4H, Ar*H*), 7.38 (t, 4H, Ar*H*, J = 8.68), 7.48 (t, 8H, Ar*H*, J = 7.55), 7.85 (t, 16H, Ar*H*, J = 7.48). ^{13}C NMR (125.7 MHz, $CDCl_3$, rt): δ (ppm) = 14.12 (CH_3), 22.68, 27.88, 29.83, 31.93 (CH_2), 37.01($CHCH_2$), 37.90 ($ArCH_2NH$), 99.67 (OCH_2O), 113.50, 120.8, 122.30, 125.22, 129.08, 129.71 (C_{aryl}), 139.48, 145.96, 148.12, 150.04, 152.99, 153. 56 (C_{aryl}). MALDI TOF-MS (Dithranol): calcd for $C_{128}H_{156}N_{12}O_8$: m/z = 1989.2 $[M]^+$; found: m/z = 2010 $[M+Na]^+$.
23-Methyl-tris(5,11,17-*p*-phenylazophenylaminomethyl)-cavitand **6**: ^{1}H NMR (500 MHz, $CDCl_3$, rt): δ (ppm) = 0.87 (t, 12H, CH_3, J = 6.94 Hz), 1.26 (m, 72H, CH_2), 1.96 (m, 3H, $ArCH_3$), 2.22 (br s, 8H, CH_2CH_2CH), 4.15 (t, 3H, N*H*), 4.2 (s, 6H, $ArCH_2NH$), 4.29 (d, 2H, OCH_2O, J = 6.91), 4.39 (d, 2H, OCH_2O, J = 6.91), 4.74 (m, 4H, $CHCH_2$), 5.97 (d, 2H, OCH_2O, J = 6.93), 6.12 (d, 2H, OCH_2O, J = 6.89), 6.76 (t, 3H, Ar*H*, J = 8.82), 6.97 (s, 2H, Ar*H*), 7.12 (s, 2H, Ar*H*), 7.37 (t, 6H, Ar*H*, J = 7.2), 7.46 (m, 6H, Ar*H*), 7.82 (m, 12H, Ar*H*). ^{13}C NMR (125.7 MHz, $CDCl_3$, rt): δ (ppm) = 12.02 ($ArCH_3$), 14.12 (CH_3), 22.60, 27.88, 29.70, 31.92 (CH_2), 37.02 ($CHCH_2$), 38.08 ($ArCH_2NH$), 99.61 (OCH_2O), 112.96, 113.32, 122.42, 125.22, 128.96, 129.69 (C_{aryl}), 138.94, 145.02, 148.08, 150.24, 152.98, 153.7 (C_{aryl}). MALDI TOF-MS (Dithranol): calcd for $C_{116}H_{147}N_9O_8$: m/z = 1797 $[M]^+$; found: m/z = 1800$[M+H]^+$.
11,23-Dimethyl-bis(5,17-*p*-phenylazophenylaminomethyl)-cavitand **7**: ^{1}H NMR (500 MHz, $CDCl_3$, rt): δ (ppm) = 0.83 (br s, 12H, CH_3,), 1.23 (m, 72H, CH_2), 1.97 (d, 6H, CH_3Ar, J = 11,31), 2.19 (br s, 8H, CH_2CH_2CH), 3.98 (br s, 2H, N*H*), 4.19 (d, 4H, CH_2NH), 4.31 (d, 4H, OCH_2O, J = 6,89), 4.77 (br s, 4H, $CHCH_2$), 5.94 (m, 4H, OCH_2O), 6.75 (t, 4H, Ar*H*, J = 8.38), 6.98 (s, 2H, Ar*H*), 7.12 (s, 2H, Ar*H*), 7.39 (m, 2H, Ar*H*), 7.47 (m, 4H, Ar*H*), 7.83 (m, 8H, Ar*H*). ^{13}C NMR (125.7 MHz, $CDCl_3$, rt): δ (ppm) = 12.02 ($ArCH_3$), 14.12 (CH_3), 22.68, 27.90, 29.82, 31.92 (CH_2), 37.00 ($CHCH_2$), 37.94 (CH_2NH), 99.02 (OCH_2O), 113.60, 119.62, 122.32, 125.09, 128.94, 129.78 (C_{aryl}), 141.00, 147.02, 149.52, 152.94, 153.04, 153. 96 (C_{aryl}). MALDI TOF-MS (Dithranol): calcd for $C_{104}H_{138}N_6O_8$: m/z = 1600.24 $[M]^+$; found: m/z = 1602 $[M+H]^+$.
11,17,23-Trimethyl-(5-*p*-phenylazophenylaminomethyl)-cavitand **8**: ^{1}H NMR (500 MHz, $CDCl_3$, rt): δ (ppm) = 0.86 (t, 12H, CH_3, J = 6.91 Hz), 1.25 (m, 72H, CH_2), 1.94 (m, 9H, $ArCH_3$), 2.20 (br s, 8H, CH_2CH_2CH), 4.06 (m, 2H, N*H*), 4.20 (d, 2H, CH_2NH, J = 8.04), 4.23 (m, 4H, OCH_2OH), 4.70 (d, 4H, $CHCH_2$), 5.89 (m, 4H, OCH_2O), 6.74 (t, 2H, Ar*H*, J = 8.56), 6.99 (s, 2H, Ar*H*), 7.10 (s, 2H, Ar*H*), 7.38 (t, 2H, Ar*H*, J = 7.37), 7.46 (t, 1H, Ar*H*, J = 7.67), 7.82 (m, 3H, Ar*H*). ^{13}C NMR (125.7 MHz, $CDCl_3$, rt): δ (ppm) = 12.02 ($ArCH_3$), 14.12 (CH_3), 22.61, 27.58, 29.79, 31.92 (CH_2), 36.95 ($CHCH_2$), 37.58 ($ArCH_2NH$), 99.67 (OCH_2O), 113.07, 113.64, 122.30, 125.22, 129.08, 129.71 (C_{aryl}), 139.48, 147.00, 148.15, 150.14, 152.89, 153.01 (C_{aryl}). MALDI TOF-MS (Dithranol): calcd for $C_{92}H_{129}N_3O_8$: m/z = 1405.02 $[M]^+$; found: m/z = 1405 $[M]^+$.