SYNTHESIS AND STRUCTURE OF NEW MACROCYCLIC BISINDOLYLMALEIMIDES

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Dedicated to the memory of Professor Otakar Červinka.

We report synthesis and structure of three new macrocyclic bisindolylmaleimides. The UV spectra of the xylene-bridged compounds **4** and **6** show significant differences. A dependence of the absorption properties on the maleimide–indole torsion angles is likely. A first attempt to use induced changes in ring conformation of the more flexible macrocyclic crown ether derivative **8** to signal the presence of metal cations failed.

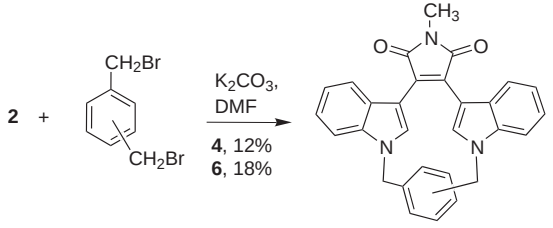
Keywords: Alkaloids; Arcyriarubine A; Indoles; Maleimides; Macrocycles; UV spectroscopy; X-ray diffraction.

Bisindolylmaleimides, such as arcyriarubine A (**1**) have been studied extensively because of their interesting pharmaceutical properties. The first arcyriarubine structure was isolated more than 20 years ago by Steglich *et al.*[1] from the fruiting bodies of the slime mould *Arcyria denudata*. Many members of this family of compounds have promising antiviral[2–5] and antimicrobial activity[6]. It has been shown that they are potent protein kinase C inhibitors[6–8]. Many derivatives of the parent bisindolylmaleimide structure have been synthesized and tested to explore the lead structure. Some recent examples are cited in refs[9–12].

The X-ray structure of **1** reveals a non-planar arrangement of the two indole moieties (Fig. 1). Its *N*-methyl derivative **2** shows similar properties in both structure and absorbance. Similarly to compound **1**, compound **2** is not planar either. The indoles are tilted out of the maleimide plane. Torsion angles between the central maleimide unit and the two indoles are different. As there are two long-wavelength absorptions in the UV spectra of **2** (365 and 453 nm, dichloromethane), the question arises as to whether UV

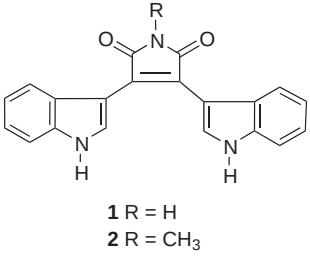
absorbance is influenced by the torsion angle. If this is the case, possible applications of **2** as a signaling group for chemosensors might be envisaged. Recognition units attached to the indole nitrogens may alter the conformation of the bisindolylmaleimide and thus alter its absorbance.

To address the question of torsion angle influence, two conformationally fixed xylene-bridged arcyriarubine derivatives **4** and **6** were synthesized to compare their UV absorbance with conformation as revealed by X-ray structure analysis and NMR spectra. Furthermore, compound **8** with a crown ether-like tetraethylene glycol unit which bridges the two indole groups was synthesized. Syntheses of compounds **4** and **6** were performed under high-dilution conditions with slow additon of starting materials *via* syringe pumps. Compound **2** was reacted with α,α′-dibromo-*p*-xylene or α,α′-dibromo-*m*-xylene (Scheme 1). Potassium carbonate was used as a base to



SCHEME 1

deprotonate the indole nitrogens in anhydrous DMF, which is indicated by a distinct color change from red to deep purple. Attempts to prepare the *o*-xylene-bridged derivative of **2** in a similar manner were not successful.



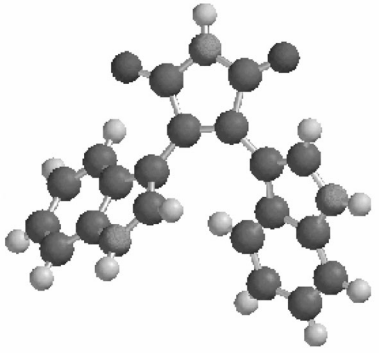


FIG. 1

Molecular structures of arcyriarubine A (**1**) and derivative **2** (left), and the structure of **1** in the crystal (right)

X-Ray structures of **4** and **6** show distinct differences (Fig. 2). Most remarkable is the almost perpendicular position of the xylene benzene unit relative to the maleimide in **4**, whereas the xylene bridge and the maleimide in compound **6** are more or less in one plane. NMR shifts of the indole protons indicate similar structures in solution. Due to the anisotropic effect of benzene ring, the proton signal of the 2 position in **4** is shifted to δ 6.11, in contrast to that in **6** where the signal is found at δ 6.94. Torsion angles in the crystal structures also differ. They were measured between the C2–C3 bond in the indole and the C3–C4 bond in the maleimide. The re-

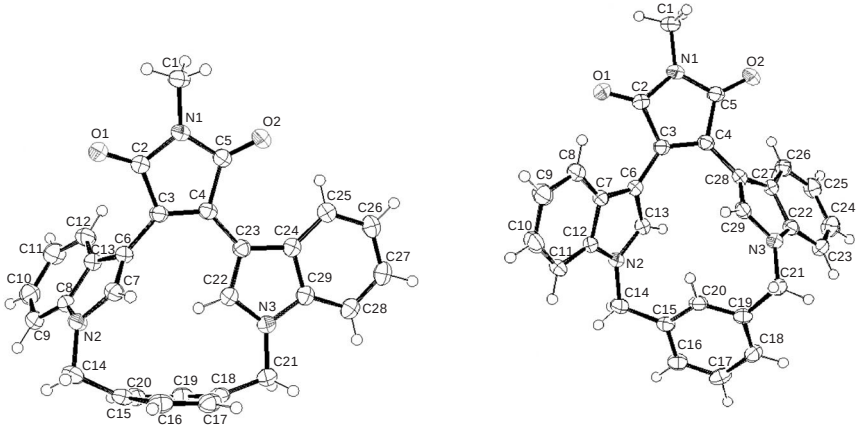


FIG. 2
X-Ray structures of **4** (left) and **6** (right)

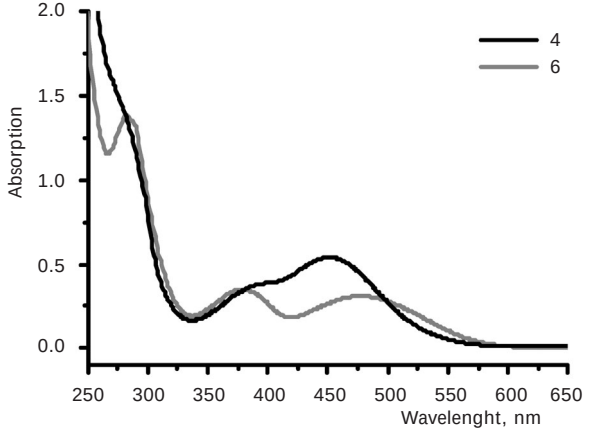


FIG. 3
Absorption spectra of **4** and **6** in dichloromethane ($c = 1 \times 10^{-4}$ mol l^{-1})

spective angles are 8.2 and 82.2° in **4**, and 40.3 and 46.9° in **6**. Hence one should expect differences in the UV spectra of **4** and **6**. As the benzene unit of the xylene bridge is not conjugated with the indoles, electronic effects on the absorption properties of **4** and **6** should be similar. However, interactions through space, such as π-stacking, cannot be excluded.

As expected, UV spectra of **4** and **6** show differences in the two long-wavelength absorptions (Fig. 3). Compound **4** has a smaller gap between two λ_{max} as it absorbs at 402 and 450 nm (the torsion angle in the X-ray structure is 74.0°), in contrast to compound **6** which shows absorption at λ_{max} = 378 and 479 nm (the torsion angle in the X-ray structure is 6.6°). The dependence of the torsion angles and the UV absorption maxima seems likely.

The simplest macrocyclic derivative which may undergo conformational changes upon guest binding is a crown ether, such as **8**. The compound was prepared starting from **2** which was reacted under standard crown ether synthesis conditions with tetraethylene glycol ditosylate **7** to form the desired macrocycle **8** with a satisfactory yield of 51% (Scheme 2).

X-Ray analysis of a suitable crystal showed that the crown ether bridge and the indole rings form a kind of pocket (Fig. 4). As reported by Gokel *et al.*[13,14] an indole unit can function as a π-donor in cation-π interactions. Thus complexation of alkali cations was regarded as feasible by the three oxygen lone pairs and additional cation-π interactions with the indole rings.

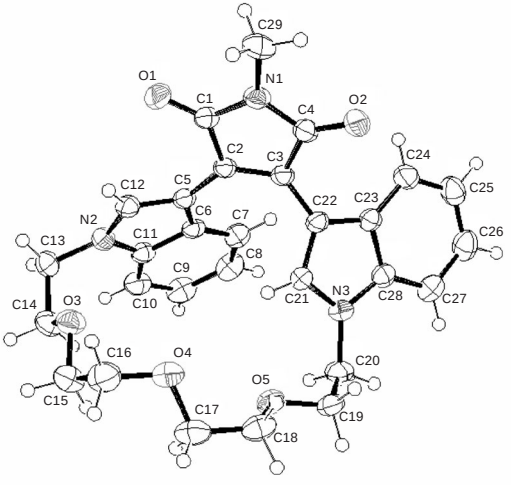
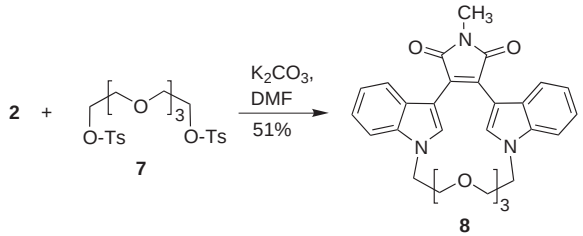


FIG. 4
Structure of compound **8** in the crystal



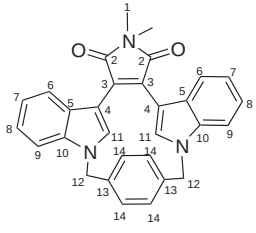
SCHEME 2

Unfortunately, the UV spectrum of **8** did not show any significant changes upon addition of up to 1000 equivalents of Li, Na, K or Cs perchlorates in acetonitrile. Changes in the emission properties of **8** were noted upon metal salt addition, but sensitivity and selectivity of the molecular recognition process are low. A likely rational for this observation is that the expected weak association of the metal cations to **8** did not induce significant conformational changes of the bisindolylmaleimide skeleton. Still, bisindolylmaleimides possessing binding sites with higher affinity may show altered absorption properties upon guest binding.

EXPERIMENTAL

Melting points were determined with a Büchi SMP 20 and are uncorrected. Thin layer chromatography (TLC) was performed on alumina plates coated with silica gel (Merck silica gel 60 F 254, layer thickness 0.2 mm). NMR spectra (δ, ppm; *J*, Hz) were recorded with a Bruker AVANCE 300 at 300 MHz (^{1}H) and 75 MHz (^{13}C) in $CDCl_3$ solutions. IR spectra (ν, cm^{-1}) were recorded with a Bio-Rad FTS 3000 MX FT-IR. MS spectra were recorded on a Varian CH-5 (EI) or a Finnigan MAT SSQ 7000 (ESI). Elemental analysis was done by the Microanalytical Laboratory of the University of Regensburg. Compounds **1** and **2** were prepared as previously described[15]. CC means column chromatography on SiO_2 (70–230 mesh from Merck).

Cyclo-*N*,*N*′-(α,α′-*para*-xylyl)bis(indol-3-yl)-*N*-methylmaleimide (**4**)

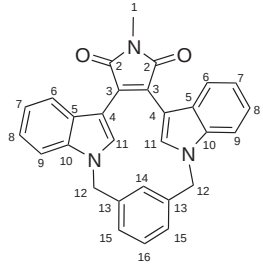


Bis(indol-3-yl)-*N*-methylmaleimide (**2**; 683 mg, 2 mmol) and α,α′-dibromo-*p*-xylene (528 mg, 2 mmol) were dissolved in 20 ml of anhydrous DMF and the solution was added to a vigorously stirred suspension of K_2CO_3 (5.5 g, 40 mmol) in 150 ml of DMF over a period of 36 h. After complete addition of the solution, it was stirred for 24 h. The mixture was poured into

150 ml of a mixture of saturated NH_4Cl solution and ice. The aqueous phase was extracted three times with 100 ml of dichloromethane, the organic phases were combined and washed with brine. After removal of the remaining water with anhydrous $MgSO_4$, the solvent was evaporated and 1.57 g of a red solid were obtained. Purification of the crude product by CC (SiO_2, CH_2Cl_2, R_F 0.7) yielded 110 mg (12%) of the desired product **4** as a red solid, m.p. 278 °C (decomp.). ^{1}H NMR ($CDCl_3$): 7.78 d, 2 H, *J*(6,7) = 8.0 (H-6); 7.48 d, 2 H, *J*(9,8) = 8.2 (H-9); 7.31 dd, 2 H, *J*(8,9) = 8.2, *J*(8,7) = 7.1 (H-8); 7.18 dd, 2 H, *J*(7,6) = 8.0, *J*(7,8) = 7.1 (H-7); 7.12 s, 4 H (H-14); 6.11 s, 2 H (H-11); 5.07 s, 4 H (H-12); 3.14 s, 3 H (H-1). ^{13}C NMR ($CDCl_3$): 170.5, 2 C (C-2); 138.2, 136.7, 130.2, 6 C (C-3, C-10, C-13); 129.4, 2 C (C-11); 129.2, 4 C (C-14); 126.2, 2 C (C-5); 121.8, 121.1, 120.0, 6 C (C-6, C-7, C-8); 108.6, 2 C (C-9); 106.1, 2 C (C-4); 49.6, 2 C (C-12); 23.1, 1 C (C-1). IR: 3154, 3115, 3045, 2941, 2882, 1758, 1695, 1530, 1438, 1377, 1244, 1199, 1156, 988, 743. MS (EI), *m/z* (rel.%): 443 (100) [M^+], 254 (11), 104 (71), 57 (10), 44 (21). HRMS (EI): for $C_{29}H_{21}N_3O_2$ calculated 443.1626, found 443.16305. UV (CH_2Cl_2), λ [nm] (ε [l mol^{-1} cm^{-1}]): 450 (5.3 × 10^3); 402 (3.8 × 10^3). Emission spectrum (CH_2Cl_2, λ_{ex} = 337 nm), λ [nm]: 627.

Crystal data: $C_{29}H_{21}N_3O_5$, M_r = 443.51, triclinic, space group *P*-1, *a* = 861.87(8) pm, *b* = 893.54(8) pm, *c* = 1426.05(14) pm, α = 79.074(11)°, β = 76.199(11)°, γ = 85.726 (11)°, *V* = 1.04669(18) nm^3, *Z* = 2, D_x = 1.407 Mg m^{-3}, λ(MoKα) = 71.073 pm, μ = 0.09 mm^{-1}, *T* = 173 K, graphite monochromator. A red prismatic crystal of 0.48 × 0.46 × 0.30 mm was measured with a STOE-IPDS-diffractometer using the rotation method. An amount of 14 859 reflexes (3800 independent reflexes, R_{int} = 0.0255) was recorded. Structure refinement: the F^2 value was refined by means of the full-matrix least-square method. The goodness of fit on F^2 value was 1.060 for all reflexes and 319 parameters. The last *R* index was *R* = 0.0370 (wR^2 = 0.0974). $\Delta\rho_{min}$ = –0.151 e Å^{-3}, $\Delta\rho_{max}$ = 0.215 e Å^{-3}.

Cyclo-*N*,*N*′-(α,α′-*meta*-xylyl)bis(indol-3-yl)-*N*-methyl-maleimide (**6**)

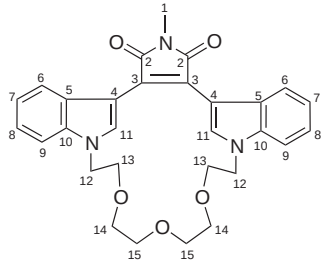


Bis(indol-3-yl)-*N*-methylmaleimide (**2**; 341 mg, 1 mmol) and α,α′-dibromo-*m*-xylene (264 mg, 1 mmol) were dissolved in 20 ml of anhydrous DMF. This solution was added to a vigorously stirred suspension of K_2CO_3 (2.25 g, 20 mmol) in 100 ml of DMF over a period of 36 h. After complete addition of the solution it was stirred for 24 h. The mixture was poured into 100 ml of a mixture of saturated NH_4Cl solution and ice. The aqueous phase was extracted three times with 100 ml of dichloromethane, the organic phases were combined and washed with brine. After removal of the remaining water with anhydrous $MgSO_4$, the solvent was evaporated and 570 mg of a red solid was obtained. Purification of the crude product by CC (SiO_2, ethyl acetate/PE 3:7, R_F 0.65) yielded 82 mg (18%) of compound **6** as a red solid, m.p. > 300 °C. ^{1}H NMR ($CDCl_3$): 7.86 dd, 2 H, *J*(6,7) = 7.4, *J*(6,8) = 1.5 (H-6); 7.41 dd,

J(9,8) = 7.5, *J*(9,7) = 1.1 (H-9); 7.31–7.17 m, 7 H (H-7, H-8, H-15, H-16); 6.94 s, 2 H (H-11); 6.55 s, 1 H (H-14); 5.15 s, 4 H (H-12); 3.24 s, 3 H (H-1). ^{13}C NMR ($CDCl_3$): 170.2, 2 C (C-2); 137.2, 136.8, 133.9, 6 C (C-3, C-10, C-13); 129.6, 125.7, 121.7, 120.3, 120.2, 10 C (C-6, C-7, C-8, C-11, C-15); 127.1, 125.8, 2 C (C-14, C-16); 126.6, 2 C (C-5); 108.7, 2 C (C-9); 104.7, 2 C (C-4); 48.4, 2 C (C-12); 23.1, 1 C (C-1). IR: 3104, 3430, 2923, 1701, 1624, 1541, 1463, 1438, 1381, 1322, 1254, 1161, 988, 730. MS (EI), *m/z* (rel.%): 443 (100) [M^+], 104 (32). HRMS (EI): for $C_{29}H_{21}N_3O_2$ calculated 443.1626, found 443.16261. UV (CH_2Cl_2), λ [nm] (ε [l mol^{-1} cm^{-1}]: 479 (3.1 × 10^3); 378 (3. × 10^3); 282 (1.4 × 10^4). Emission spectrum (CH_2Cl_2, λ_{ex} = 419 nm), λ [nm]: 644.

Crystal data: $C_{29}H_{21}N_3O_5$, M_r = 443.51, monoclinic, space group *P*21/*a*, *a* = 1127.02(7) pm, *b* = 1639.59(12) pm, *c* = 1199.12(8) pm, α = 90°, β = 108.226(7)°, γ = 90°, *V* = 2.1046(3) nm^3, *Z* = 4, D_x = 1.400 Mg m^{-3}, (MoKα) = 71.073 pm, μ = 0.089 mm^{-1}, *T* = 173 K, graphite monochromator. A red platelike crystal of 0.30 × 0.24 × 0.04 mm was measured with a STOE-IPDS-diffractometer using the rotation method. An amount of 19 057 reflexes (4944 independent reflexes, R_{int} = 0.1075) were recorded. Structure refinement: the F^2 value was refined by the full-matrix least square method. The goodness of fit on F^2 value was 0.814 for all reflexes and 307 parameters. The last *R* index was *R* = 0.0490 (wR^2 = 0.0954). $\Delta\rho_{min}$ = –0.190 e Å^{-3}, $\Delta\rho_{max}$ = 0.231 e Å^{-3}.

Cyclo-*N*,*N*′-(1,11-(3,6,9-trioxaundecyl))bis(indol-3-yl)-*N*-methylmaleimide (**8**)



Bis(indol-3-yl)-*N*-methylmaleimide (**2**; 309 mg, 0.9 mmol) was dissolved in 350 ml DMF and K_2CO_3 (4.50 g, 30 mmol) was added. Tetraethylene glycol ditosylate (**7**; 502 mg, 1.0 mmol) dissolved in 50 ml of DMF was added to the stirred suspension at 50 °C over a period of 48 h. Stirring was continued for 5 h. Then the reaction mixture was cooled to room temperature, poured into 600 ml of a saturated NH_4Cl solution and ice. The aqueous phase was extracted four times with 150 ml of ethyl acetate, and the combined organic phases were washed twice with 100 ml of water. After drying with anhydrous $MgSO_4$, the solvent was evaporated. The remaining red solid was purified by CC (SiO_2; PE/ethyl acetate 15:85, R_F 0.26) and recrystallized from ethanol/water 8:2 to yield 229 mg (51%) of compound **8** as red prisms, m.p. 197–198 °C. ^{1}H NMR ($CDCl_3$): 7.60 s, 2 H (H-11); 7.36–7.29 m, 4 H (H-7, H-8); 7.22–7.15 m, 2 H (C-9); 7.02–6.95 m, 2 H (C-6); 4.24 t, 4 H, *J*(12,13) = 4.6 (H-12); 3.65 t, 4 H, *J*(13,12) = 4.6 (H-13); 3.19 s, 3 H (H-1); 3.19–3.16 m, 8 H (H-14, H-15). ^{13}C NMR ($CDCl_3$): 172.4, 2 C (C-2); 137.2, 2 C (C-3); 132.2, 2 C (C-11); 127.8, 125.1, 4 C (C-5, C-10); 122.7, 122.0, 120.1, 6 C (C-6, C-7, C-8); 109.7, 2 C (C-9); 106.1, 2 C (C-4); 71.6, 71.0, 70.6, 6 C (C-13, C-14, C-15); 45.7, 2 C (C-12); 24.1, 1 C (C-1). IR: 3049, 2867, 1753, 1698, 1537, 1386, 1124, 1100, 744. MS (EI), *m/z* (rel.%): 499 (100) [M^+], 43 (24), 28 (47). UV (CH_2Cl_2),

λ [nm] (ε [l mol^{-1} cm^{-1}]): 474 (8.6 × 10^3); 385 (6.0 × 10^3); 279 (1.4 × 10^4). Emission spectrum (CH_2Cl_2, λ_{ex} = 346 nm), λ [nm]: 637. For $C_{29}H_{29}N_3O_5$ (499.6) calculated: 69.72% C, 5.85% H, 8.41% N; found: 69.48% C, 5.74% H, 8.24% N.

Crystal data: $C_{29}H_{29}N_3O_5$, M_r = 499.55, monoclinic, space group *P*21/*n*, *a* = 1115.96(9) pm, *b* = 1136.65(6) pm, *c* = 2072.98(15) pm, α = 90°, β = 103.902(9)°, γ = 90°, *V* = 2.5525(3) nm^3, *Z* = 4, D_x = 1.300 Mg m^{-3}, λ(MoKα) = 71.073 pm, μ = 0.09 mm^{-1}, *T* = 173 K, graphite monochromator. A red primatic crystal of 0.44 × 0.36 × 0.16 mm was measured with a STOE-IPDS-diffractometer using the rotation method. An amount of 22 129 reflexes (4819 independent reflexes, R_{int} = 0.0585) were recorded. Structure refinement: the F^2 value was refined by the full-matrix least square method. The goodness of fit on F^2 value was 0.880 for all reflexes and 334 parameters. The last *R* index was *R* = 0.0382 (wR^2 = 0.0865). $\Delta\rho_{min}$ = –0.193 e Å^{-3}, $\Delta\rho_{max}$ = 0.226 e Å^{-3}.

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