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Biscyclohexane-Annulated Diethyl Dipyrrindicarboxylates: Observation of a Dipyrrin Form with Absent Visible Absorption

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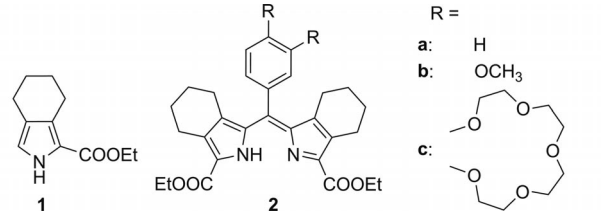
A series of 2,3;7,8-biscyclohexano-fused diethyl 5-aryldipyrrin-1,9-dicarboxylates have been synthesized [aryl = phenyl, 3,4-dimethoxyphenyl and 2,3,5,6,8,9,11,12-octahydro-1,4,7,10,13-benzopentaoxacyclopentadecine-15-yl (*m*-benzo-15-crown-5)]. The obtained compounds were shown to exist in two equilibrium forms in solution, with one exhibiting a visible absorption band (λ_{abs} 468–485 nm), and the other, "vis-silent" form, having no absorption band in the visible region. The "vis-silent" form has been isolated and characterized by NMR analysis, including two-dimensional techniques. Quantum chemical calculations have also been performed, yielding two main conformations with proximate and distant arrangements of the nitrogen atoms. In the latter conformation the pyrrole–pyrrolene fragments were found to be nearly orthogonal, with no long chain of conjugation. Computational results confirm the spectroscopic findings. Two different forms were also characterized as their Mg^{2+} complex and investigated by UV/Vis and by NMR spectroscopic analyses and a clear difference was noted.

Introduction

Dipyrrins as their boron difluoride complexes (BODIPY) have been known since the end of 1960s.[1] Their high extinction coefficient and fluorescence properties facilitated their applications in areas such as, but not limited to, biochemistry labeling[2] and laser dyes.[3] BODIPY compounds have also been used as the signaling part of sensors in a multitude of systems.[4,5] Metal-free dipyrrins were also studied as ligands for prospective organometallic systems,[6,7] including those with potential sensor properties.[8–10]

Absorption and fluorescence properties of dipyrrins are dependent on the type of substituents. These may enlarge the π-system[9,11] leading to a redshift of the band maxima in the optical spectra. Substituents may also turn on or off various mechanisms for excited state relaxation.[4] For example, *meso*-phenyl-substituted BODIPY dyes exhibit much stronger fluorescence when a substituent is attached at the pyrrole or the phenyl[12] ring that hinders rotation of the phenyl group.

Because our group has been interested in the study of brominated palladium tetrabenzoporphyrins,[13] we have access to the key intermediate in their synthesis, i.e., tetrahydroisoindole carboxylic acid ester **1**. This intermediate is also a precursor of the corresponding dipyrrin.[6] The purpose of this study was therefore the synthesis and investigation of new *meso*-substituted biscyclohexano-fused dipyrrin derivatives, including a potentially ditopic receptor **2c**, as well as its "non-macrocyclic" and "π-neutral" analogues **2b** and **2a**, respectively. In addition to being conformationally restricted, dipyrrins of type **2** include an annelated cyclohexane ring moiety that invokes high distortion of the porphyrins, which make them highly basic.[14] These features of the studied substances could enhance their complexation and/or sensor properties.



Recently, several accounts on cyclohexano-annulated BODIPY compounds have appeared,[15] in addition to earlier works devoted to bicyclo[2.2.2]octene derivatives by Ono et al.[10] Garrido Montalblan et al. succeeded in the synthesis of dipyrrin-1,10-dicarboxylate and its boron complexes.[16] However, to the best of our knowledge, no report on the sensing properties of dipyrrins themselves with the cyclohexano-annulated pyrrole exist, with the exception of a very recently released patent application by Cheprakov and Vinogradov et al.[17]

Results and Discussion

Starting dipyrromethanes were synthesized according to the literature procedure.[18] Oxidation of dipyrromethanes

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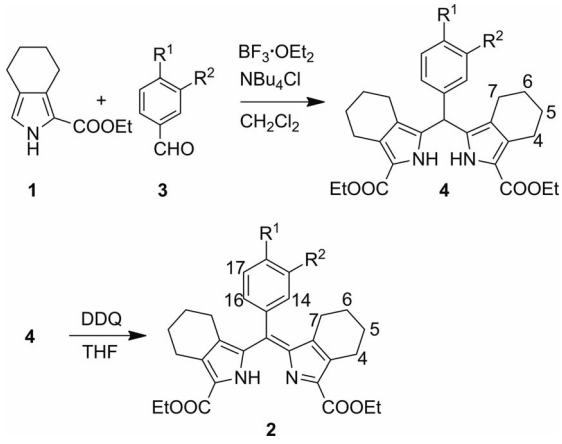
to dipyrrins by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) proceeded smoothly for compounds with donor aryl substituents in the *meso* positions. Compounds **4b** and **4c** were consumed in two hours to form pure **2b** and **2c**, respectively (Scheme 1). However, 10% of the unsubstituted phenyl compound **4a** remained unaffected after three hours reaction; longer reaction times resulted in partial oxidation of the cyclohexane ring (according to NMR and MALDI analyses). Thus, pure **2a** was obtained after the residual **4a** was removed from the reaction mixture by washing with hexane.



Scheme 1. The synthesis of dipyrrins.

^{1}H NMR spectroscopic analysis of the pure samples of **2a**–**c** revealed two sets of signals (denoted as "Set I" and "Set II", Figure 1) for each chemical group. In different experiments, the isolated product contained these signals in arbitrarily different integral intensity ratios. However, in the case of **2c**, this ratio reached ca. 7:1 after standing in $CHCl_3$ solution.

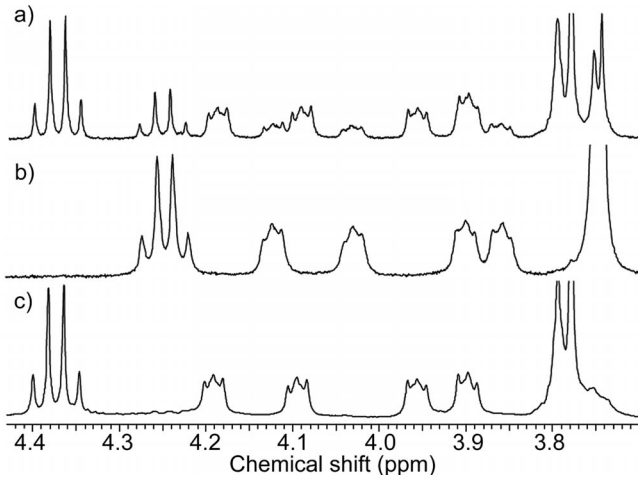


Figure 1. ^{1}H NMR spectra of **2c** in the CH_2O region. (a) Isolated sample (mixture of the sets); (b) after slow crystallization from hexanes (Set II); (c) after treatment with CF_3COOH/Et_3N (Set I).

We succeeded in isolating one of the components and obtained samples possessing just one set in their ^{1}H NMR spectra. Slow crystallization from hexane yielded a pink, amorphous substance that gave a colorless solution showing only the Set II signals (Figure 1, b). Conversely, addition of trifluoroacetic acid to the solution followed by its neutralization with triethylamine produced the spectrum with only Set I (Figure 1, c).

^{1}H NMR spectra of **2** had clear signals that could be attributed to the aromatic rings and OCH_2 groups according to their positions, multiplicity and integral intensities. For example, OCH_2CH_3 quadruplets appeared at δ = 4.25 and 4.37 ppm for the **2c** Set II and Set I components. Crown ether signals in Set II were systematically shifted upfield with respect to those of Set I. NMR analysis of the phenyl region also reveal an upfield shift of H-16 and H-17 in Set II, whereas its H-14 resonance was placed 0.08 ppm downfield compared to the same proton in Set I. NOESY experiments (see the Supporting Information, Figures S6d and S7a) confirmed these assignments.

Signals of methylene groups from the cyclohexane rings (Figure 2) were assigned by COSY (see the Supporting Information, Figures S4 and S5) experiments. They show more pronounced differences; i.e., the Set II signals appear at δ = 2.79, 1.66, 1.54–1.58 and 1.97 ppm, which are quite close to those of dipyrromethane **4c** (δ = 1.62–1.68, 2.13 and 2.77 ppm; see Figure 2). However, Set I features two upfield shifted resonances at δ = 1.37 ppm (overlapping with the CH_3 of the ethoxycarbonyl) and 1.62 ppm, whereas the signals at δ = 1.59 and 2.68 ppm, resembling their analogues in the Set II, were found.

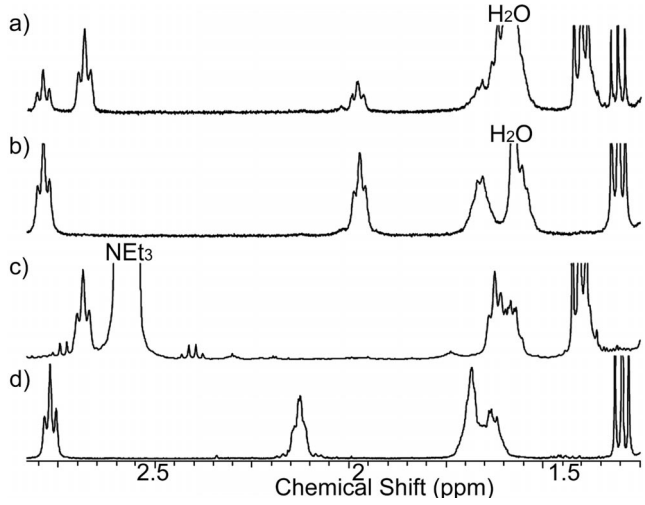


Figure 2. ^{1}H NMR spectra of the cyclohexane ring region of **2c**. (a) Isolated sample; (b) the Set II component; (c) after CF_3COOH/Et_3N treatment (Set I); (d) the same region for **4c**.

Both the optical spectra and the color of Set I and Set II solutions were strikingly different (Figure 3). Set II, the "colorless" solution, gave rise to only a UV band in the UV/Vis spectrum, whereas Set I, the "red" component, exhibited an intense band at 472 nm (CH_3CN) in the visible region. Addition of acid to the solutions caused the instant emergence of a band at 524 nm. These values are close to those of protonated and nonprotonated dipyrrins.[19] Compounds **2a** and **2b** show the same ^{1}H NMR (Table 1) and UV/Vis (Table 2) features.

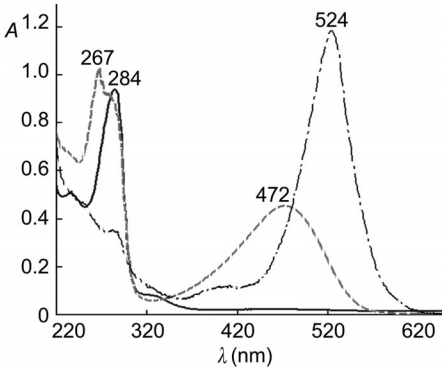


Figure 3. UV/Vis spectra of **2c** (in CH_3CN) for samples exhibiting Set I (dashed line) or Set II (solid line) resonances in the NMR, and Set II after addition of excess $HClO_4$ (dotted-dashed line).

Table 1. ^{1}H NMR spectra of compounds **2a**–**c**.

	Component	^{1}H NMR[a]			
		Ph[b]	OCH_2 CH_3	other OCH_2[c]	*cyclo*-C_6[d]
2a	red	7.24-7.27, 7.43-7.45	4.38, 1.41	–	2.68, 1.49–1.52, 1.35, 1.58
(2:1)[e]	colorless	7.28-7.30, 7.34-7.36	4.24, 1.30	–	2.79, 1.66, 1.53–1.59, 1.96
2b (5:1)	red	6.76, 6.82, 6.92	4.38, 1.41	3.85, 3.95	2.70, 1.59, 1.39, 1.64
	colorless	6.74, 6.82, 6.92	4.25, 1.31	3.88, 3.79	2.80, 1.64, 1.58, 2.01
2c (7:1)	red	6.75, 6.79, 6.90	4.37, 1.40	4.19, 4.09, 3.96, 3.90, 3.78–3.80	2.68, 1.59, 1.37, 1.62
	colorless	6.87, 6.73, 6.80	4.25, 1.31	4.12, 4.03, 3.90, 3.86, 3.74–3.75	2.79, 1.66, 1.54–1.58, 1.97

[a] Signals of cyclohexane methylene groups were attributed by COSY experiments (see the Supporting Information, Figures S1–S5); those of the phenyl groups, CH_3CH_2 of ethoxycarbonyls, and crown ether signals were assigned on the basis of their shapes, their characteristic spin systems, and by relative integral intensities. [b] Given in the order H-14, H-16, H-17 for 3-substituted rings. [c] CH_2 groups being closer to the phenyl ring are listed first; those being equally close are listed in order R^1 then R^2. [d] In the order H-4, H-5, H-6, H-7. [e] Equilibrium ratio (at room temperature) of the components according to NMR integrals of OEt quadruplets.

Table 2. UV/Vis spectra of compounds **2a**–**c**.

	Component	
2a	mixture (“set I”/“set II” ca 2:1)	264 (1), 468 (0.65)[a]
2b	mixture (“set I”/“set II” ca 4:1)	283 (1), 473 (0.10)
2c	mixture (“set I” “set II” ca. 4:1)	267 (1), 472 (0.44)
	colorless (“set II”)	284

[a] Relative intensity.

The components differ in their physical properties; for example, the Set II (colorless) component of all the studied mixtures were better soluble in hexane than the Set I (red) component. In contrast, solubility in acetonitrile showed the opposite trend; for example, washing **2a** with hexane left primarily the “red” component (14:1 “red” to “colorless” ratio, NMR), which gradually reverted to a 2:1 equilibrium ratio in solution (the ratio for **2b** was 5:1). The components could also be discriminated by TLC (see the Exp. Section). In addition, after being separated along one direction in 2D TLC, each spot gave rise to a second pair of the same spots along the second direction.

Kinetics of the interconversion between **2cI** (the Set I component) and **2cII** (Set II component) was measured at 300 K. The rate constant of the **2cI** to **2cII** reaction and that of the reverse have been estimated to be 7×10^{-6} and 1×10^{-6} s^{-1}, respectively (see the Supporting Information).

The data may be interpreted as the interconversion between two different conformations of each species; indeed, such transformations have long been known[20] [*Note:* In view of fast degenerate proton migration that causes a switch between two double bond arrangements in the dipyrrin, we refer to these spatial transformations as *conformational* changes. Rotation about the *meso*-pyrrole single bond in one arrangement becomes *E*–*Z* isomerization of the *meso*-pyrrolene double bond in the other. Thus, we will use the term “conformations”, meaning different positions of the tetrahydroisoindole fragments with respect to each other. The double bond arrangement also formally influences the name of the ring annelated to the pyrrole/pyrrolene moieties (“cylcohexano” or “cyclohexeno”). For the sake of clarity we refer these rings to as “cyclohexano”.] This interconversion has been the subject of theoretical calculations.[21] Furthermore, a series of thorough studies of biliverdin and its synthetic analogues have been performed in relation to their helical structure.[22] Dipyrrinone derivatives have been shown to form the *E* isomer depending on the substituent at the carbon[23] or at the nitrogen atoms.[24]

The observed spectra possess two significant features. First, the absence of the absorption band in the visible region for one of the conformers leads to the assumption that there is no efficient overlap between pyrrolic chromophores in the molecule. Second, the number of NMR signals in both “colorless” and “red” conformers correspond to effectively symmetrical structures, i.e., each group in the tetrahydroisoindole fragments yield only one type of ^{1}H NMR resonance.

To gain insight into the possible orientation of different parts of the molecules, we performed geometry optimization of unsubstituted dimethyl ester **2d** at the HF/6-31(d) level of theory. The results of the computation yields nonsymmetrical structures (see Figure 4, and the Supporting Information Table S2). Both of these are featured by the in-plane arrangement of the ester groups with respect to the pyrrole and pyrrolene rings. The dipyrrin moiety in the *cis-syn* conformation (Figure 4, a, and the Supporting Information Table S2) is nearly flat and, therefore, has the expected overlap of a pyrrole–pyrrolene π-system. In contrast,

the *trans-anti* conformation has a dihedral angle between the planes of the pyrrole and pyrrolene rings equal to 69.9 ° (Figure 4, b, and the Supporting Information Table S2), precluding efficient overlap.

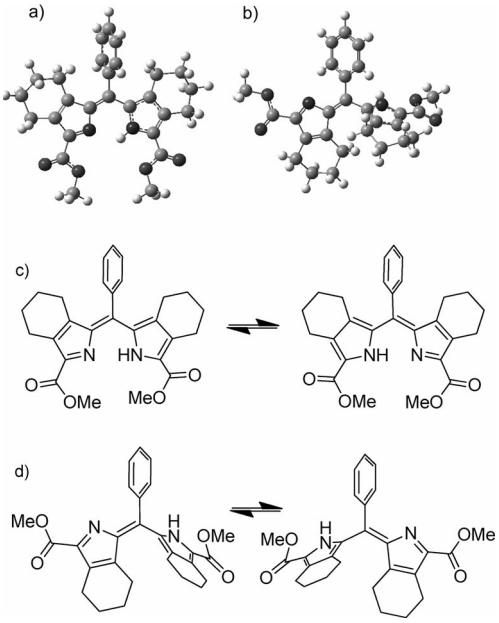


Figure 4. Results of geometry optimization at the HF/6-31(d) level for the conformers of (a) **2dI**, (b) **2dII** (for details see the Supporting Information), and a corresponding schematic representation of their degenerate spatial reorganization in (c) **2dI** and (d) **2dII**.

The effective symmetry observed for each conformation can be the result of proton exchange. Despite the *cis-syn* conformations being slightly twisted in solution,[25] such exchange is very efficient both in solution[20] and in the crystal.[26] Effective symmetry for the *trans-anti*-**2** demands that the proton migration should be accompanied by substantial rotation of each of the pyrrole–pyrrolene fragments (Figure 4).

The computational results are in accord with the NMR experiments. NOESY spectra reveal clear cross-peaks between the signals of the NH-protons and the phenyl *ortho*-protons for "colorless", *trans-anti* conformer **2cII** (see the Supporting Information, Figure S6a). In addition, *ortho*-protons are close to one of the methylene groups of the cyclohexane ring, which is also manifested by the corresponding cross-peak (see the Supporting Information, Figure S6c).

Furthermore, protons of the methylene groups in the "red", *cis-syn* form **2cI** are in the anisotropy region of the phenyl substituent, resulting in an upfield shift of their ^{1}H NMR signals. No such upfield resonances are observed for **2cII**; its cyclohexane ring resonances are reasonably close to those observed for **4c** (see above).

The nearly orthogonal arrangement of the pyrrole–pyrrolene fragments, and the absence of a visible absorption in the studied compounds is a novel feature of dipyrrins that has not been previously observed. For instance, three conformations (*cis-syn*, *cis-anti* and *trans-anti*) of dipyrrins have been reported by Dolphin et al.[27] X-ray data and spectroscopic studies in solution indicate that efficient overlap between the pyrrole and pyrrolene moieties exists. However, an approximately 30° angle between the pyrrole–pyrrolene planes is observed for the *cis-anti* conformation due to steric hindrance caused by C- and N-bonded hydrogen atoms. Hindrance caused by the cyclohexane rings in the compounds studied in this paper is much more severe, which causes considerable deviation of the fragments from the main dipyrrin plane and much slower interchange rate, making the conformers visible in solution at room temperature.

The closest analogues of the studied substances are dipyrrins annulated to cyclic unsaturated[9] or bicyclic fragments,[10] which have been used as precursors for new, highly emissive fluorophores. However, no similar conformational transformations have been mentioned.

UV/Vis and NMR Complexation Studies

We also performed some experiments to examine the receptor properties of **2cI** and **2cII**. The ratio of the components gradually changes with time and/or possibly with the addition of the analyte. Thus, only qualitative changes of the UV/Vis spectra can be discussed. To test these properties, Mg^{2+} was chosen for two reasons: (1) Mg salts are known to form complexes with both dipyrrin and crown

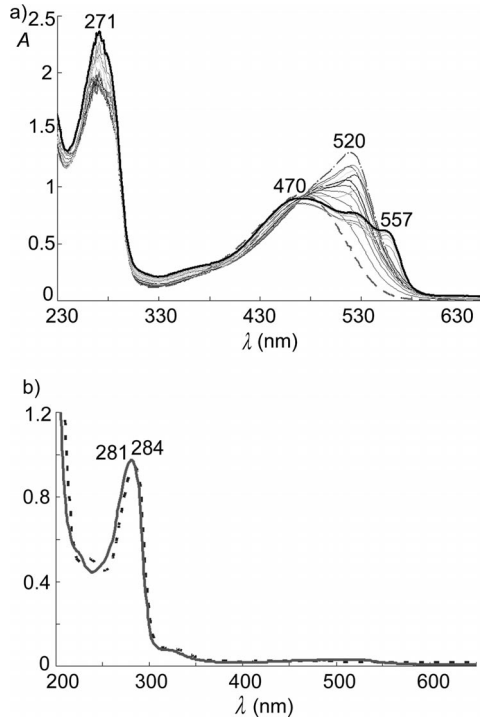


Figure 5. Changes in the absorption spectra of **2c** in CH_3CN upon addition of $Mg(ClO_4)_2$. (a) To the mixture of **2cI** and **2cII** ca. 2:1 ($c = 2.5 \times 10^{-7}$ M): before addition of $Mg(ClO_4)_2$ (dashed line), after addition of twofold excess of $Mg(ClO_4)_2$ (dotted-dashed line), after addition of 300-fold excess of $Mg(ClO_4)_2$ (solid line). (b) **2cII**: before addition of $Mg(ClO_4)_2$ (dotted line), after addition of ca. 50-fold excess of $Mg(ClO_4)_2$ (solid line).

ether fragments;[6,28] (2) we found that these salts do not cause fast conformer interconversion.

Addition of magnesium perchlorate to solutions of **2cI** and **2cII** in acetonitrile led to the following changes in the visible region of the spectrum (Figure 5). An isosbestic point was apparent at low concentration of the salt, indicating that the site of complexation and dipyrrin conformation are invariable, i.e., the dye forms the only complex with the metal ion. Absorption maximum is, as expected, shifted to the red region. As the concentration of the salt was increased, however, the development of new bands was seen at even longer wavelengths. Under these conditions, the isosbestic point disappears, indicating additional complexation processes. In contast, no substantial change in the UV/Vis spectrum of the **2cII** solution was found upon addition of the Mg^{2+} salt.

NMR studies on the complex formation corroborate the optical spectroscopic findings. They reveal that chemical shifts of the crown ether and phenyl protons of both **2cI** and **2cII** undergo a substantial change upon the addition of $Mg(ClO_4)_2$. However, the change of the proton resonances of the cyclohexane moiety indicates that only the dipyrrin system of **2cI** is involved in complex formation (see the Supporting Information and Figure S9).

Conclusions

Representatives of 2,3;7,8-biscyclohexano-fused diethyl 5-aryldipyrrin-1,9-dicarboxylates have been synthesized, namely, one possessing an unsubstituted phenyl group (Ph) and derivatives substituted with π-donors. Two conformations have been observed for all three compounds in solution. The first, "regular" conformer exhibits a visible band at ca. 470 nm, whereas the second, "vis-silent" form has no visible band in the optical spectrum. Steric hindrance has been shown to be responsible for disrupting the conjugation in the "vis-silent" conformation. These forms have different complexation behavior with respect to magnesium ions.

Experimental Section

General: Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. ^{1}H (400 MHz, HMDS as internal standard) and ^{13}C (100 MHz, $CDCl_3$ as internal standard) NMR spectra were obtained with a Bruker Avance 400 instrument. 2D NOESY spectra were measured with a Bruker Avance 600 spectrometer. $CDCl_3$ was kept over dehydrated molecular sieves for at least 48 h prior to spectra acquisition. Elemental analyses were performed by the Laboratory of Microanalysis of the Chemistry Department of Moscow State University. Melting points were obtained with a capillary melting point apparatus Mel-TempII in open-ended capillaries and are uncorrected. The UV/Vis spectra were recorded with an Agilent-8453 spectrophotometer. Laser desorption ionization (LDI-TOF) Mass spectra were recorded with a Bruker Daltonics Autoflex II. Samples were irradiated with a nitrogen laser (λ = 337 nm) and an accelerating voltage of 19 kV. The theoretical calculation of intensity distribution of isotope peaks was performed using the program IsotopeViewer Version 1.0. Quantum mechanical calculations were performed by using the Gaussian 03[29] program with a 6-31(d) Hamiltonian. For details, see the Supporting Information.

General Procedure for the Preparation of the Dipyrromethanes: Aldehyde (1 equiv.), ethyl 4,5,6,7-tetrahydro-2*H*-isoindole-4-carboxylate **1** (2 equiv.) and tetrabutylammonium chloride (0.15 equiv.) were dissolved in distilled CH_2Cl_2 and degassed with a stream of Ar for 30 min. Freshly distilled $BF_3{\cdot}Et_2O$ (0.2 equiv.) was then added by using a syringe and the solution was stirred under Ar at room temperature for 6 h until no more starting aldehyde could be detected by TLC analysis (TLC spots were visualized by 0.5% 2,4-dinitrophenylhydrazine/2 M HCl, eluent CH_2Cl_2 or EtOAc). The reaction mixture was washed with 10% aqueous Na_2CO_3, water, and brine, and dried with Na_2SO_4. Removal of the solvent under vacuum gave a solid that was recrystallized from hexane or purified by column chromatography.

Diethyl 3,3′-(Phenylmethylene)bis(4,5,6,7-tetrahydro-2*H*-isoindole-1-carboxylate) (4a): Prepared according the general procedure with benzaldehyde (0.26 mL, 2.59 mmol, freshly distilled), **1** (1 g, 5.18 mmol), Bu_4NCl (0.108 g, 0.39 mmol), and $BF_3{\cdot}Et_2O$ (0.066 mL, 0.52 mmol) in CH_2Cl_2 (50 mL). Removal of the solvent gave a light-orange solid. The product was recrystallized from hexane, giving **4a** (0.91 g, 74% yield) as a white solid; m.p. 158–159 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.27 (t, J = 7.1 Hz, 6 H, -CH_3), 1.63–1.70 [m, 8 H, -$CH_2(CH_2)_2CH_2$-], 2.17 [m, 4 H, -$CH_2(CH_2)_2$-CH_2-], 2.77 [m, 4 H, -$CH_2(CH_2)_2CH_2$-], 4.19 (q, J = 7.1 Hz, 4 H, -OCH_2CH_3), 5.39 (s, 1 H, CH), 7.08 (m, 2 H, ArH), 7.24–7.31 (m, 3 H, ArH), 8.59 (br. s, 2 H, NH) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.49, 21.26, 23.16, 23.33, 40.62, 59.71, 116.77, 119.75, 127.26, 128.20, 128.89, 129.22, 130.78, 139.04, 161.76 ppm. LDI-TOF: m/z = 473.09 [M – H]$^+$, 497.06 [M + Na]$^+$, 513.00 [M + K]$^+$. $C_{29}H_{34}N_2O_4$ (474.59): calcd. C 73.39, H 7.22, N 5.90; found C 73.09, H 7.02, N 5.41.

Diethyl 3,3′-[(3,4-Dimethoxyphenyl)methylene]bis(4,5,6,7-tetrahydro-2*H*-isoindole-1-carboxylate) (4b): Prepared according the general procedure with 3,4-dimethoxybenzaldehyde (0.2144 g, 1.29 mmol), **1** (0.4986 g, 2.58 mmol), Bu_4NCl (0.0528 g, 0.19 mmol), and $BF_3{\cdot}Et_2O$ (0.033 mL, 0.26 mmol) in CH_2Cl_2 (25 mL). Removal of the solvent gave an orange solid. The product was purified by chromatography on silica gel (CH_2Cl_2); yield 0.64 g (93%); m.p. 110–112 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.28 (t, J = 7.0 Hz, 6 H, -OCH_2CH_3), 1.63–1.72 [m, 8 H, -$CH_2(CH_2)_2CH_2$-], 2.16 [m, 4 H, -$CH_2(CH_2)_2CH_2$-], 2.77 [m, 4 H, -$CH_2(CH_2)_2CH_2$-], 3.77 (s, 3 H, -OCH_3), 3.86 (s, 3 H, -OCH_3), 4.20 (q, J = 7.0 Hz, 4 H, -OCH_2CH_3), 5.33 (s, 1 H, CH), 6.60 (m, 2 H, ArH), 6.79 (d, J = 8.4 Hz, 1 H, ArH), 8.58 (br. s, 2 H, NH) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.52, 21.25, 23.14, 23.32, 40.58, 55.88, 55.93, 59.71, 111.47, 116.55, 119.62, 120.43, 129.31, 130.82, 131.15, 148.30, 149.32, 161.69 ppm. LDI-TOF: m/z = 533.04 [M – H]$^+$, 557.01 [M + Na]$^+$, 572.94 [M + K]$^+$. $C_{31}H_{38}N_2O_6$ (534.64): calcd. C 69.64, H 7.16, N 5.24; found C 69.19, H 7.09, N 4.68.

Diethyl 3,3′-(2,3,5,6,8,9,11,12-Octahydro-1,4,7,10,13-benzopentaoxacyclopentadecin-15-ylmethylene)bis(4,5,6,7-tetrahydro-2*H*-isoindole-1-carboxylate) (4c): Prepared according the general procedure with 2,3,5,6,8,9,11,12-octahydro-1,4,7,10,13-benzopentaoxacyclopentadecine-15-carbaldehyde (0.3052 g, 1.03 mmol), **1** (0.3981 g, 2.06 mmol), Bu_4NCl (0.0417 g, 0.15 mmol), and $BF_3{\cdot}Et_2O$ (0.027 mL, 0.21 mmol) in CH_2Cl_2 (25 mL). Removal of the solvent gave an orange solid. The product was purified by chromatography on silica gel (EtOAc); yield 0.47 g (69%); m.p. 118–119 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.30 (t, J = 7.1 Hz, 6 H, -OCH_2CH_3), 1.62–1.68 [m, 8 H, -$CH_2(CH_2)_2CH_2$-], 2.13 [m, 4 H, -$CH_2(CH_2)_2CH_2$-], 2.77 [m, 4 H, -$CH_2(CH_2)_2CH_2$-], 3.74 (m, 8 H,

-OCH_2-), 3.86 (m, 2 H, -OCH_2-), 3.90 (m, 2 H, -OCH_2-), 4.03 (m, 2 H, -OCH_2-), 4.11 (m, 2 H, -OCH_2-), 4.23 (q, J = 7.1 Hz, 4 H, -OCH_2CH_3), 5.28 (s, 1 H, CH), 6.60 (m, 2 H, ArH), 6.79 (d, J = 8.8 Hz, 1 H, ArH), 8.32 (br. s, 2 H, NH) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.52, 21.21, 23.08, 23.28, 40.51, 59.71, 68.54, 68.62, 69.05, 69.13, 70.18, 70.60, 113.76, 113.82, 116.54, 119.62, 121.15, 129.38, 130.65, 131.82, 147.90, 148.92, 161.63 ppm. LDI-TOF: m/z = 663.14 [M – H]$^+$, 687.13 [M + Na]$^+$. $C_{37}H_{48}N_2O_9$ (664.79): calcd. C 66.85, H 7.28, N 4.21; found C 66.61, H 7.15, N 4.10.

General Method for the Preparation of the Dipyrrins: The dipyrromethane (1 equiv.) was dissolved in anhydrous THF and degassed with a stream of Ar for 20 min. A solution of DDQ (2 equiv.) in anhydrous THF was then added by using a syringe. The solution was stirred under Ar at room temperature for 2 h, then the reaction mixture was diluted with CH_2Cl_2, washed with 10% aqueous Na_2SO_3, 10% aqueous Na_2CO_3, water, and brine. The organic layer was separated, dried with Na_2SO_4, and the solvents were evaporated to dryness.

Ethyl 1-{[3-(Ethoxycarbonyl)-4,5,6,7-tetrahydro-2*H*-isoindol-1-yl]-(phenyl)methylene}-4,5,6,7-tetrahydro-1*H*-isoindole-3-carboxylate (2a): Compound **4a** (0.100 g, 0.211 mmol) in THF (10 mL) and DDQ (0.0958 g, 0.422 mmol) in THF (2 mL) were reacted according to the general procedure for 3 h,giving mixture of **2aI**, **2aII**, and the initial **4a** in a ratio of 9:1:1 according to NMR spectroscopy. After washing with hexane (50 mL), a mixture of **2aI**, **2aII** (0.062 g, 0.13 mmol, 62%) was isolated as an orange powder. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (mixture of isomers **2aI** and **2aII** in a ratio of 12:1; integral intensities are given for the conformers that were observed in more than 10:1 excess) = 1.35 [m, 4 H, -$CH_2(CH_2)_2CH_2$- of **2aI**], 1.41 (t, J = 7.0 Hz, 6 H, -OCH_2CH_3 of **2aI**), 1.49–1.52 [m, 4 H, -$CH_2(CH_2)_2CH_2$- of **2aI**], 1.52–1.59 [m, 4 H, -$CH_2(CH_2)_2CH_2$- of **2aI**], 2.68 [m, 4 H, -$CH_2(CH_2)_2CH_2$- of **2aI**], 4.38 (q, J = 7.0 Hz, 4 H, -OCH_2CH_3 of **2aI**), 7.24–7.27 (m, 2 H, ArH of **2aI**), 7.43–7.45 (m, 3 H, ArH of **2aI**), 8.69 (br. s., 1 H*, NH of **2aII**), 13.06 (br. s, 1 H*, NH of **2aI**) ppm. [* Integral intensities of the exchanging protons make up 0.6–0.8 of the theoretical value.] ^{1}H NMR ($CDCl_3$, 400 MHz): δ (mixture of isomers **2aI** and **2aII** in a ratio of 2:1) = 1.30 (t, J = 7.0 Hz, -OCH_2CH_3 of **2aII**), 1.35 [m, -$CH_2(CH_2)_2CH_2$- of **2aI**], 1.41 (t, J = 7.0 Hz, -OCH_2CH_3 of **2aI**), 1.49–1.52 [m, -$CH_2(CH_2)_2CH_2$- of **2aI**], 1.53–1.59 [m, -$CH_2(CH_2)_2CH_2$- of **2aI** and **2aII**], 1.66 [m, -$CH_2(CH_2)_2CH_2$- of **2aII**], 1.96 [m, -$CH_2(CH_2)_2CH_2$- of **2aII**], 2.68 [m, -CH_2-$(CH_2)_2CH_2$- of **2aI**], 2.79 [m, -$CH_2(CH_2)_2CH_2$- of **2aII**], 4.24 (q, J = 7.0 Hz, -OCH_2CH_3 of **2aII**), 4.38 (q, J = 7.0 Hz, -OCH_2CH_3 of **2aI**), 7.24–7.27 (m, ArH of **2aI**), 7.28–7.30 (m, ArH of **2aII**), 7.34–7.36 (m, ArH of **2aII**), 7.43–7.45 (m, ArH of **2aI**), 8.70 (br. s, NH of **2aII**), 13.02 (br. s, NH of **2aI**) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ (mixture of isomers **2aI** and **2aII** in a 5:1 ratio) = 14.39, 14.49, 22.07, 22.37, 22.97, 23.09, 23.18, 23.23, 23.35, 24.25, 59.80, 60.56, 116.36, 119.75, 126.85, 128.43, 128.65, 128.71, 128.80, 129.06, 129.55, 132.66, 133.02, 137.05, 139.09, 139.62, 141.82, 142.01, 144.17, 161.55, 162.32 ppm. R_f = 0.74 (**2aI**), 0.26 (**2aII**) ($CHCl_3$/EtOH = 50:1; SiO_2). LDI-TOF: m/z = 472.99 [M + H]$^+$, 510.91 [M + K]$^+$. $C_{29}H_{32}N_2O_4$ (472.24): calcd. C 73.70, H 6.83, N 5.93; found C 73.59, H 6.88, N 5.81.

Ethyl (1*Z*)-1-{(3,4-Dimethoxyphenyl)[3-(ethoxycarbonyl)-4,5,6,7-tetrahydro-2*H*-isoindol-1-yl]methylene}-4,5,6,7-tetrahydro-1*H*-isoindole-3-carboxylate (2b): Compound **4b** (0.300 g, 0.561 mmol) in THF (15 mL) and DDQ (0.2547 g, 1.122 mmol) in THF (5 mL) were reacted according to the general procedure to give **2b** (0.2898 g, 97%) as a red powder. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (mixture of isomers **2bI** and **2bII** in a ratio of 4:1) = 1.31 (t, J = 7.1 Hz, -OCH_2CH_3 of **2bII**), 1.41 [m, J = 7.1 Hz, -OCH_2CH_3 and -$CH_2(CH_2)_2CH_2$- of **2bI**], 1.56–1.64 [m, -$CH_2(CH_2)_2CH_2$- of **2bI** and **2bII**], 2.01 [m, -$CH_2(CH_2)_2CH_2$- of **2bII**], 2.70 [m, -CH_2-$(CH_2)_2CH_2$- of **2bI**], 2.80 [m, -$CH_2(CH_2)_2CH_2$- of **2bII**], 3.79 (s, -OCH_3 of **2bII**), 3.85 (s, -OCH_3 of **2bI**), 3.88 (s, -OCH_3 of **2bII**), 3.95 (s, -OCH_3 of **2bI**), 4.25 (q, J = 7.1 Hz, -OCH_2CH_3 of **2bII**), 4.38 (q, J = 7.1 Hz, -OCH_2CH_3 of **2bI**), 6.74–6.76 (m, ArH of **2bI** and **2bII**), 6.81–6.83 (m, ArH of **2bI** and **2bII**), 6.92 (m, ArH of **2bI** and **2bII**), 8.71 (br. s, NH of **2bII**), 12.73 (br. s, NH of **2bI**) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ (mixture of isomers **2bI** and **2bII** in a 7:1 ratio) = 14.33, 22.38, 23.07, 23.15, 24.36, 55.83, 56.05, 60.54, 111.12, 111.96, 121.84, 129.26, 132.97, 139.21, 139.48, 141.59, 144.21, 149.28, 149.86, 162.27 ppm (signals of isomer **I** only observed in ^{13}C NMR spectrum if the conformer ratio is higher than 6:1). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (mixture of isomers **2bI** and **2bII** in a 3:1 ratio) = 14.33, 14.42, 21.92, 22.38, 22.93, 23.07, 23.15, 23.21, 23.34, 24.36, 55.79, 55.81, 55.83, 56.05, 59.81, 60.54, 110.08, 110.59, 111.12, 111.96, 116.09, 119.44, 119.69, 121.84, 128.77, 128.82, 129.26, 132.97, 133.16, 134.51, 139.21, 139.48, 141.59, 144.21, 148.86, 148.92, 149.28, 149.86, 161.69, 162.27 ppm. R_f = 0.9 (**2bI**), 0.3 (**2bII**) ($CHCl_3$, Al_2O_3). LDI-TOF: m/z = 533.04 [M + H]$^+$, 555.01 [M + Na]$^+$, 570.97 [M + K]$^+$. $C_{31}H_{36}N_2O_6$ (532.63): calcd. C 69.90, H 6.81, N 5.26; found C 69.74, H 6.89, N 4.85.

Ethyl (1*Z*)-1-{[3-(Ethoxycarbonyl)-4,5,6,7-tetrahydro-2*H*-isoindol-1-yl](2,3,5,6,8,9,11,12-octahydro-1,4,7,10,13-benzopentaoxacyclopentadecin-15-yl)methylene}-4,5,6,7-tetrahydro-1*H*-isoindole-3-carboxylate (2c): Compound **4c** (0.300 g, 0.451 mmol) in THF (15 mL) and DDQ (0.2048 g, 0.902 mmol) in THF (5 mL) were reacted according to the general procedure. The product was recrystallized from hexane to give **2c** (0.2571 g, 86%) as a red powder. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (isomer **2cI**) = 1.40 [m, J = 7.2 Hz, 10 H, -OCH_2CH_3 and -$CH_2(CH_2)_2CH_2$-], 1.57–1.64 [m, 8 H, -CH_2-$(CH_2)_2CH_2$-], 2.68 [m, 4 H, -$CH_2(CH_2)_2CH_2$-], 3.78–3.80 (m, 8 H, -OCH_2-), 3.90 (m, 2 H, -OCH_2-), 3.96 (m, 2 H, -OCH_2-), 4.09 (m, 2 H, -OCH_2-), 4.19 (m, 2 H, -OCH_2-), 4.37 (q, J = 7.2 Hz, 4 H, -OCH_2CH_3), 6.75 (m, J = 1.8 Hz, 1 H, ArH), 6.79 (m, J_1 = 1.8, J_2 = 8.1 Hz, 1 H, ArH), 6.90 (m, J = 8.1 Hz, 1 H, ArH), 12.86 (br. s, 1 H*, NH) ppm. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (isomer **2cII**) = 1.31 (t, J = 7.1 Hz, 6 H, -OCH_2CH_3), 1.54–1.58 [m, 4 H, -$CH_2(CH_2)_2CH_2$-], 1.66 [m, 4 H, -$CH_2(CH_2)_2CH_2$-], 1.97 [m, 4 H, -$CH_2(CH_2)_2CH_2$-], 2.79 [m, 4 H, -$CH_2(CH_2)_2CH_2$-], 3.74–3.75 (m, 8 H, -OCH_2-), 3.86 (m, 2 H, -OCH_2-), 3.90 (m, 2 H, -OCH_2-), 4.03 (m, 2 H, -OCH_2-), 4.12 (m, 2 H, -OCH_2-), 4.25 (q, J = 7.1 Hz, 4 H, -OCH_2CH_3), 6.73 (m, J_1 = 1.7, J_2 = 8.3 Hz, 1 H, ArH), 6.80 (d, J = 8.3 Hz, 1 H, ArH), 6.87 (m, J = 1.7 Hz, 1 H, ArH), 8.70 (br. s, 1 H*, NH) ppm. [* Integral intensities of the exchanging protons make up 0.6–0.8 of the theoretical value.] ^{13}C NMR ($CDCl_3$, 100 MHz): δ (mixture of isomers **2cI** and **2cII** in a ratio of 8:1) = 14.42, 22.45, 23.14, 23.22, 24.50, 60.58, 68.34, 68.85, 69.31, 70.11, 70.13, 71.01, 113.14, 114.25, 122.20, 129.67, 133.06, 139.31, 139.64, 141.73, 144.16, 149.27, 149.96, 162.39 ppm (signals of isomer **I** only observed in the ^{13}C NMR spectrum if the conformer ratio is higher than 6:1). ^{13}C NMR ($CDCl_3$, 100 MHz, –20 °C): δ (isomer **2cII**) = 14.37, 21.57, 22.74, 23.02, 23.33, 60.05, 67.82, 67.94, 68.96, 69.01, 69.74, 70.44, 111.53, 111.59, 115.71, 119.78, 119.85, 128.76, 128.99, 132.68, 134.51, 148.31, 148.82, 161.01 ppm. R_f = 0.44 (**2cI**), 0.3 (**2cII**) ($CHCl_3$/EtOH = 15:1; SiO_2). LDI-TOF: m/z = 663.17 [M + H]$^+$, 685.16 [M + Na]$^+$, 701.11 [M + K]$^+$. $C_{37}H_{46}N_2O_9$ (662.77): calcd. C 67.05, H 7.00, N 4.23; found C 66.76, H 6.72, N 4.32.

Supporting Information (see footnote on the first page of this article): 2D NMR spectra of the studied compounds; kinetic measure-

ments of **2c** conformer exchange; QC computation details; NMR spectra response to Mg^{2+} complexation.

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