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Novel peptidomimetic macrocycles showing exciplex fluorescence

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Abstract—The synthesis of five new chiral macrocyclic peptidomimetic naphthalenophanes, together with two open-chain derivatives, is described. The cyclization step is accomplished in good yields without the use of high dilution or template techniques. The new compounds have been photophysically studied by means of steady-state fluorescence spectroscopy. It has been found that the smaller the ring size, the higher the emission quantum yield from the excited charge-transfer state (CTS, exciplex) and the lower the fluorescence from the locally excited state (LES). The occurrence of exciplex fluorescence is noteworthy as the electron-donating groups are secondary amine moieties, which do not normally form emissive exciplexes.

1. Introduction

Macrocyclic molecules have attracted great attention with consideration of their interesting properties as ligands able to form complexes with cations, anions and neutral molecules.[1] They have found applications in diverse areas like medicinal,[2] analytical[3] or supramolecular chemistry.[4] Among macrocycles, those containing amines or amides (poly-aza or poly-amido macrocycles, respectively) must be synthesized according to specific procedures that are different to those required for the poly-oxa macrocyclic compounds.[5] Since the initial reports on macrocyclic polyamines by Stetter and Roos[6] a great number of strategies have been developed for the synthesis of this class of compounds, including high dilution conditions, templation and use of conformationally preorganized macrocycle precursors.[5,7,8] Recently we have developed a new methodology for the synthesis of poly-(amino-amido) macrocycles.[9] This methodology has been successfully employed to synthesize families of chiral compounds for: molecular probes for cellular studies;[10] minimalistic peptidomimetic organogelators;[11] a fluorescent sensor for amino acid derivatives;[12] selective receptors for Ag(I);[13] and molecular rotors.[14] Among the molecules synthesized using this protocol a fluorescent macrocycle containing a 1,4-dimethylnaphthalene fluorophore, two L-valine subunits, and a three-methylene spacer (**1b** in Chart 1) was described.[11b,12,15] The emission spectrum of **1b** in dichloromethane was remarkably red-shifted (ca. 50 nm) with respect to the expected fluorescence of the parent naphthyl subunit, due to the formation, upon excitation, of an emissive intramolecular excited-state charge-transfer complex (exciplex) between a secondary amine (electron donor) and the aromatic moiety (electron acceptor).[15] The fluorescence quantum yield of such an emissive exciplex was determined to be 0.038 in dichloromethane, which is surprisingly high for an arene-secondary amine exciplex. Normally, primary and secondary amines do not form fluorescent exciplexes at room temperature but deactivate through the proton-transfer pathway.[16] It was *hypothesized* that this anomalous value was due to the rigidity of the macrocycle, which provided the special conditions for the occurrence of such phenomenon.[15] As a consequence of this previous report a series of questions are raised: (a) Is the macrocycle necessary for the formation of an emissive exciplex?; (b) Given a macrocycle with N members, will the $N-1$ be more fluorescent than the N, and the $N+1$ less emissive?; (c) To what extent are the lateral chains pending from the ring important?, are they neutral elements not involved in the formation–decay of the exciplex or play a role in the fine tuning of the energetics of ground and excited states? For the formation of an emissive exciplex a delicate balance between numerous factors must be attained, many of which are based on speculation, as is recognized in the literature.[17–21] In order to answer the above questions, while minimizing the speculative aspects, measurements of molecules similar to but slightly modified versions of **1b** were required.

This work describes the synthesis and chemical characterization of seven new chiral compounds (five macrocyclic, **1a**, **1c**, **2a**–**c**, and two open-chain derivatives, **3** and **4**; see

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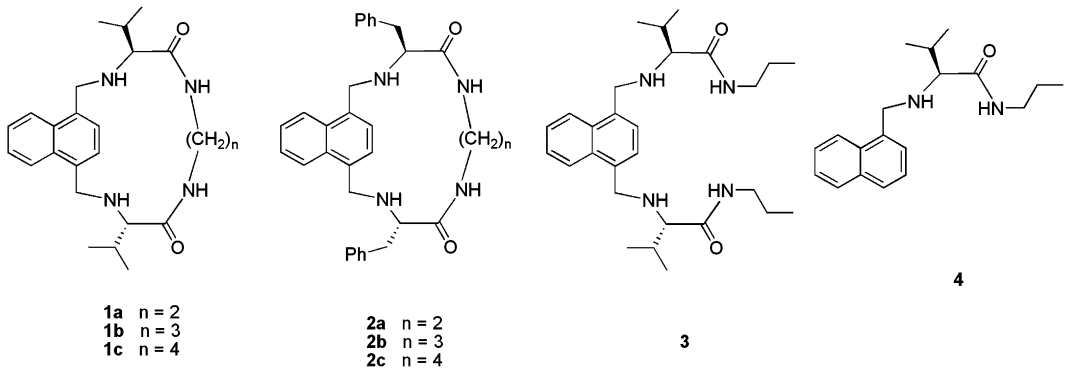


Chart 1.

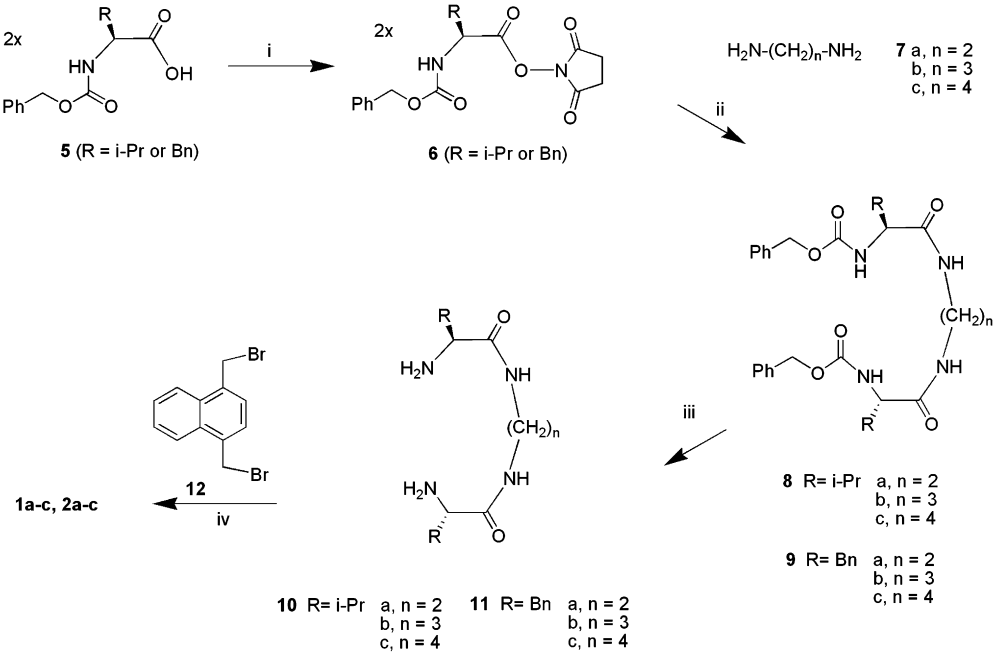
Chart 1) having a naphthyl chromophore and one or two amino-amide moieties (derived from L-valine or from L-phenylalanine). The macrocyclic compounds have been obtained using the previously mentioned methodology[9] in moderate-good yields. The fluorescence quantum yields in dichloromethane have been determined and discussed. With this synthetic/photochemical study a double objective was attained: on the one hand the family of *photoactive macrocycles* developed in our group[8,10,11b,12,15] has been expanded with five new members and, on the other hand, it provides some insight into the relationships between structure and the photophysical properties of poly-azacyclophanes.[22]

2. Results and discussion

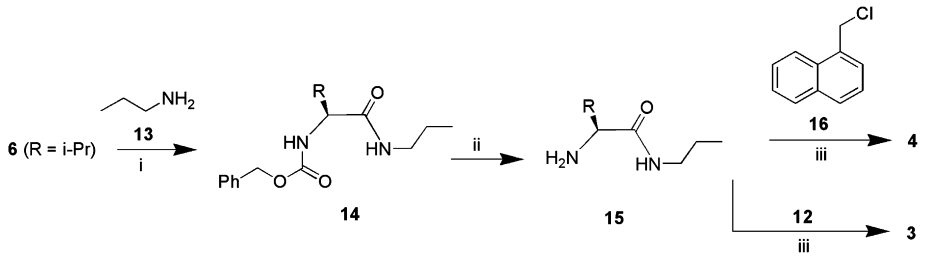
2.1. Synthesis

The synthesis of macrocycles **1a–c** and **2a–c** is outlined in Scheme 1. Product **1b** has been previously reported.[11b,12,15] The commercially available N-Cbz protected L-amino acids (**5**, from valine or phenylalanine) were transformed into the activated *N*-hydroxysuccinimide esters (**6**) and then coupled with the corresponding 1,*n*-alkanediamine (**7a–c**). After removal of the protecting groups from **8a–c** and **9a–c**, the open-chain peptidomimetic compounds **10a–c** and **11a–c** were obtained in an overall 60–80% yield.[9] The macrocyclization step was accomplished by reacting **10a–c** and **11a–c** with 1,4-bis(bromomethyl)naphthalene (**12**) in anhydrous acetonitrile, using potassium carbonate as base, and tetrabutylammonium bromide as phase transfer catalyst. The crude reaction products were purified by column chromatography to afford the pure macrocycles. The open-chain derivatives were synthesized analogously to **1a–c** and **2a–c** by using *n*-propylamine (**13**) instead of a 1,*n*-dialkylamine (for **3** and **4**) and 1-(chloromethyl)naphthalene (**16**) instead of 1,4-bis(bromomethyl)naphthalene (for **4**) (Scheme 2).

The yield for the cyclization step of **1a–c** and **2a–c** is in the range 20–41%, which can be considered as moderately-good. The difference with the previously reported *para* and *meta*-phenylene derivatives (45–69% cyclization yield) could



Scheme 1. Synthesis of **1a–c** and **2a–c**. Conditions: (i) DCC, *N*-hydroxysuccinimide, THF, 0–5 °C; (ii) DME, 40–50 °C; (iii) HBr/AcOH, rt; and (iv) CH_3CN, K_2CO_3 reflux.



Scheme 2. Synthesis of **3** and **4**. Conditions: (i) THF, reflux; (ii) HBr/AcOH, rt; and (iii) CH_3CN, reflux.

be related to the different volumes of the aromatic spacer (naphthyl vs phenyl).[23] If compared with other non-templated macrocyclization reactions yielding cyclic amino-amides the overall synthesis of **1a–c** and **2a–c** is advantageous since very high dilution conditions need not be employed (typically 10 mM was used for these reactions whereas for other systems concentrations of ~1 mM or lower are normally reported[24]). In fact, macrocycles are obtained as white solids at a quasi-gram scale (typically 300–700 mg was synthesized for every compound). These good yields can be explained, as previously analyzed in detail,[9] considering intramolecular H-bonds and solvophobic effects inducing a favorable (folded) conformation of the reactants in acetonitrile.

2.2. Photophysical studies

The electronic absorption spectra of naphthalenophanes (**1a–c**) and open-chain derivatives **3** and **4** in dichloromethane are depicted in Figure 1. As it can be seen, the smallest macrocycle **1a** displays a broader and red-shifted (291 nm) absorption profile as compared to the open-chain derivative **3** (288 nm); whereas the largest macrocycle **1c** matches the absorption of **3** (288 nm). The macrocycle **1b** shows an absorption, which is intermediate (290 nm) between **1a** and **1c**. The absorption of **4** is blue-shifted, presumably due to the different substitution in the aromatic chromophore. The differences observed between these macrocycles are indicative of the influence of the ring size on the electronic properties of their ground states, although fluorescence spectroscopy will provide more information of the upper excited states. More remarkable is the absence of any charge-transfer (CT) absorption band at long wavelengths in any of the spectra, since all these (with the exception of **4**) match the absorption of 1,4-dimethylnaphthalene (not shown). This would indicate that population of the state responsible for the exciplex emission[15] cannot be done directly but only by means of excitation of the upper singlet states. Regarding the macrocycles derived from L-phenylalanine (**2a–c**), similar spectra were obtained from these compounds (max. at 289–290 nm) (Fig. 2), again with no significant CT absorption band. The different patterns observed in valine derivatives (gradual shifting) versus phenylalanine derivatives (almost identical position of the maxima) suggest a differing influence of the lateral chain in the conformational stability of both series of compounds.

The corrected fluorescence spectra of **1a–c**, **3**, and **4** in dichloromethane, upon excitation at 300 nm, are shown in Figure 3. Although the absorption spectra of these compounds did not afford substantial information (Fig. 1), interpretation of the emission spectra gives some clues to address the questions posed earlier. In first instance, fluorescence emission from **1a** (391 nm) and **1b** (389 nm) are almost identical and can be attributed to an excited charge-transfer state (CTS, exciplex) as previously noted.[15] Only a minimal difference can be seen: the profile of **1a** emission is practically a perfect Gaussian curve whereas that of **1b** displays some irregularity in the 320–350 nm region. In that

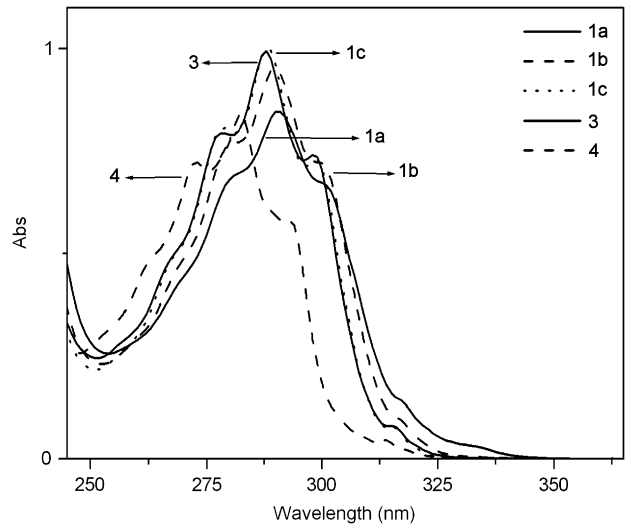


Figure 1. Absorption spectra of compounds **1a–c**, **3**, and **4** in dichloromethane (concentration: 1.3×10^{-4} M).

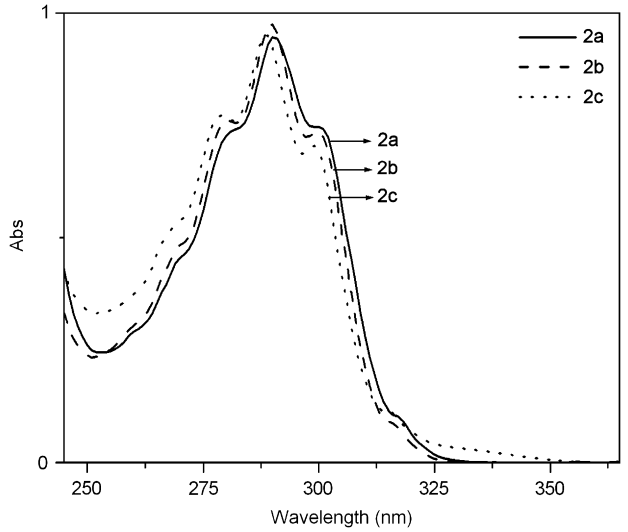


Figure 2. Absorption spectra of compounds **2a–c** in dichloromethane (concentration: 1.3×10^{-4} M).

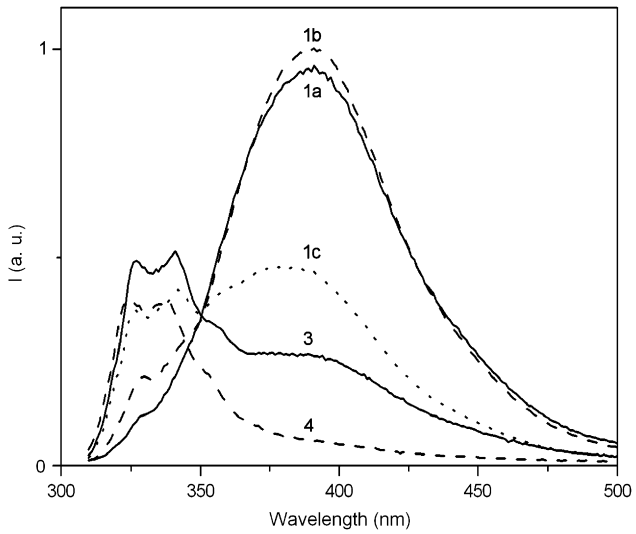


Figure 3. Corrected fluorescence spectra of compounds **1a–c**, **3**, and **4** in dichloromethane.

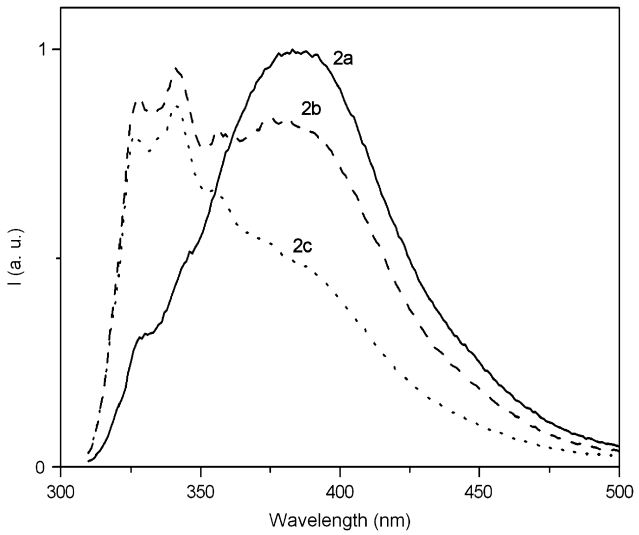


Figure 4. Corrected fluorescence spectra of compounds **2a–c** in dichloromethane.

wavelength region, it was shown that the emission arises from the locally excited state (LES), or S_1, of the 1,4-dimethylnaphthalene moiety. This residual fluorescence from LES (<0.001)[15] in **1b** is absent in **1a**. When the macrocycle is one unit larger (**1c**) the fluorescence from the CTS falls to one half of **1a** or **1b** and an appreciable emission from the LES is observed. Comparing to the non-cyclic derivative **3**, which could be formally considered as a macrocycle with $n=\infty$, the same tendency is followed, i.e., a decrease of the CTS emission and an increase of the LES fluorescence. Finally, the monoamine **4** only displays very weak emission from the LES. The absence of CTS emission from **4** is in accordance with the paradigm about exciplexes in arene-secondary amine systems, i.e., fluorescence from LES of arene-secondary amine systems can be partially quenched but does not lead to any exciplex emission at room temperature. However, spectra of **1a–c** and **3** suggest a redefinition of such a statement. These results confirm experimentally that emissive exciplexes from secondary amines are not impossible at room temperature, and, most importantly, they can be *finely tuned* by adjusting the ring size of the macrocycle. Even non-cyclic compounds like **3**, while having two electron-donor groups, can display exciplex emission.

The group of naphthalenophanes derived from L-phenylalanine shows a similar tendency in qualitative terms: the smaller the ring size, the higher the fluorescence intensity from the CTS, as can be seen in Figure 4. Noteworthy, both exciplex emission and emission from the LES are weak in the case of the largest macrocycle **2c**. This would mean that, on the one hand, the emissive CTS is either not forming as efficiently as for **2a** or its radiationless decay is more efficient, and, on the other hand, the photoinduced electron-transfer (PET) mechanism is operating to quench the emission from the LES,[25] probably to yield directly the *solvent separated* radical anion (naphthyl moiety) and radical cation (amine) pair. In this case solvation of the radical ions would be limited by the covalent link between donor and acceptor, which would make back-electron transfer (BET) very fast.

Comparing both series of peptidomimetic cyclophanes, **1a–c** vs **2a–c**, it can be seen how the differences depend on the ring size. For the smallest cycles, **1a** and **2a**, there is a reasonable coincidence of shape and position of CTS fluorescence spectra (Fig. 5), with **2a** slightly blue-shifted compared to **1a**. Additionally, the LES emission, absent in **1a**, is incipiently emerging in **2a**. This small difference is amplified in the medium-sized molecules, becoming apparent for the comparison between **1b** and **2b** (Fig. 6), and more clearly for **1c** and **2c** (Fig. 7). Thus, not only the ring size is important to account for the emission of the CTS but also the appended chains. A question that remains to be elucidated is the role of the intramolecular H-bonding pattern (between amines and/or amides) in solution, as the strong influence of this pattern on the stability of different conformers for analogous macrocycles has been previously demonstrated.[14,26] However, this analysis would only give a partial view of the picture (H-bonding of the amine lone-pairs, geometrical orientation, and orbital overlapping, for instance)

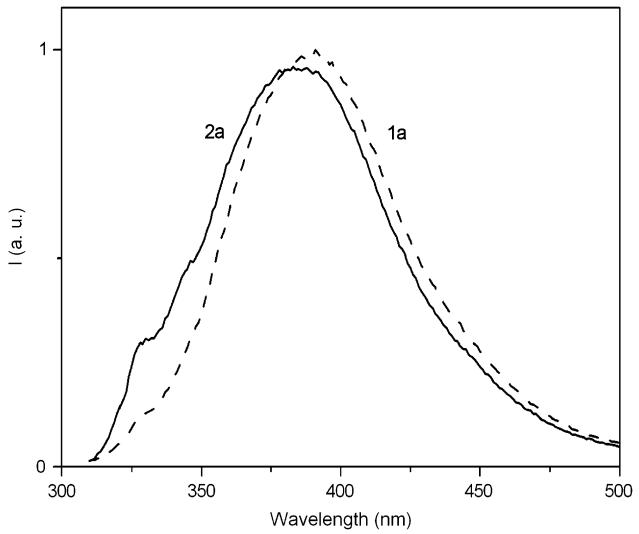


Figure 5. Corrected fluorescence spectra of compounds **1a** and **2a** in dichloromethane.

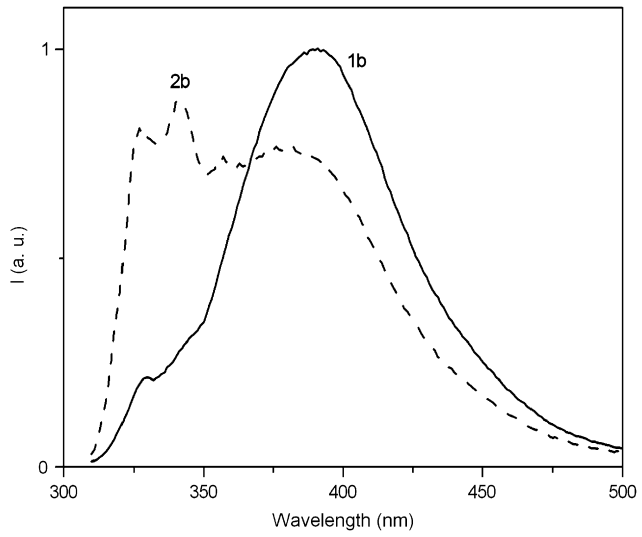


Figure 6. Corrected fluorescence spectra of compounds **1b** and **2b** in dichloromethane.

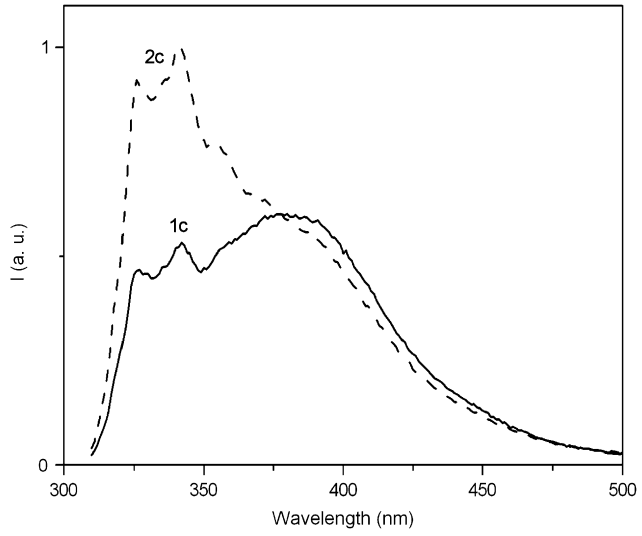


Figure 7. Corrected fluorescence spectra of compounds **1c** and **2c** in dichloromethane.

since it would not provide information about deactivation pathways of the excited states (for instance intersystem crossing (ISC) or back-electron transfer (BET) from the CTS).

In order to know the relative contributions of LES and CTS to the total emission, deconvolution of curves into pure LES and pure CTS was done. In this way, the percentage of photons coming from both emitting states can be determined (Table 1). On the other hand, since the fluorescence quantum yield of **1b** has been previously measured and since all the emissions were taken in isoabsorptive conditions, the total emission quantum yields (LES+CTS) were determined by calculating the areas under the curves and comparing to that of the reference (**1b**) (Table 1). Hence, with %LES and ϕ_{em} (total) the emission quantum yield from such a state (ϕ_{em} (LES)), and analogously from the charge-transfer state (ϕ_{em} (CTS)) can be calculated.

The higher values of ϕ_{em} (CTS) are those corresponding to macrocycles **1a** (0.037), **1b** (0.038), and **2a** (0.031), decreasing considerably for medium and large macrocycles (0.019–0.009). For the open-chain **3** the value of 0.005 (29% of the total fluorescence), although low, points to the possibility of the following occurring: (a) temporary intramolecular H-bonding between both amide groups leading to a stable conformation (pseudo-cyclic) favorable for the deactivation of the CTS via fluorescence; or (b) triplex emission, which would require both amines to be concurrently oriented toward the aromatic ring, as described for some anthracenic systems.[27] A plot of ϕ_{em} (CTS) and ϕ_{em} (total) vs size of the macrocyclic compound (*N*) is shown in Figure 8. As it can be seen, decreasing the size of the macrocycle increases the fluorescence (total and from the exciplex) but ~0.040 seems to be a limit, at least for these families of cyclophanes. Finally, the emission from LES is always much less important than that expected from an unquenched naphthalene. In fact, when **1b** is fully protonated with HCl, and hence is PET hampered, emission from LES reaches 0.130, as shown previously.[15]

3. Conclusion

The aim of this work was the description of the synthesis of some new peptidomimetic naphthalenophanes in order to: (a) add new chiral cyclophanes to the known pool of photoactive macrocycles, which could be used in the future as chiral receptors for species of biological interest (amino acids), as reported for **1b**;[12] and (b) to confirm that the anomalous emission of **1b** is not a unique case. To fully understand the ultimate reason for the differences between macrocycles, the results presented here will be complemented with future additional photophysical measurements (time resolved

Table 1. Photophysical parameters of compounds **1a–c**, **2a–c**, **3**, and **4**: maxima absorption and emission wavelength for the LES and CTS in dichloromethane; total and partial (LES or CTS) fluorescence quantum yields (excitation at 300 nm)

Entry	Compound	λ_{abs}/nm	λ_{em} (LES)/nm	λ_{em} (CTS)/nm	% LES	% CTS	ϕ_{em} (total)	ϕ_{em} (LES)	ϕ_{em} (CTS)
1	**1a**	291	—	391	0	100	0.037	—	0.037
2	**1b**	290	—	389	<2	>98	0.038	<0.001	0.038
3	**1c**	288	342	379	47	53	0.023	0.011	0.012
4	**2a**	290	—	383	18	82	0.038	0.007	0.031
5	**2b**	290	341	382	52	48	0.039	0.020	0.019
6	**2c**	289	341	380 (sh)	66	34	0.027	0.018	0.009
7	**3**	288	341	380 (sh)	71	29	0.018	0.013	0.005
8	**4**	282	337	—	100	0	0.009	0.009	—

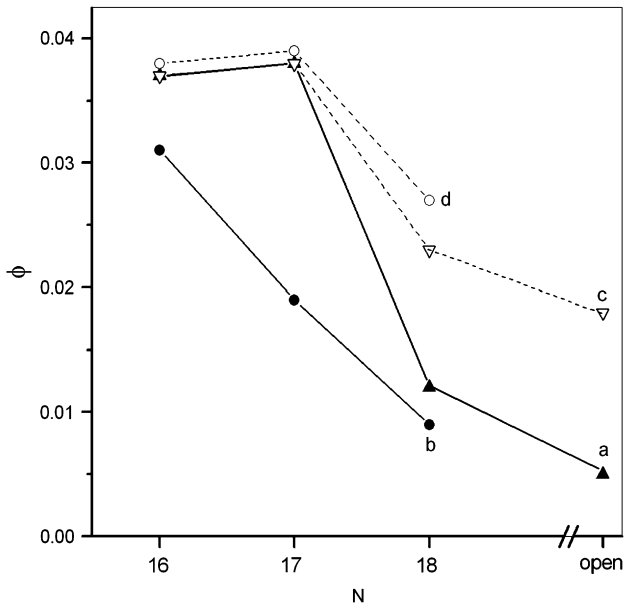


Figure 8. Fluorescence quantum yields of compounds **1a–c**, **2a–c**, and **3** in dichloromethane. *N* Represents the total number of atoms in the ring of cyclophanes **1a–c** and **2a–c**. Open-chain derivative has been introduced out of scale (or $N=\infty$). (a) ϕ_{em} (CTS) for valine derivatives; (b) ϕ_{em} (CTS) for phenylalanine derivatives; (c) ϕ_{em} (total) for valine derivatives; and (d) ϕ_{em} (total) for phenylalanine derivatives.

fluorescence or laser flash photolysis) since multiple processes affect not only the ground state (intramolecular hydrogen bonding) but also the excited states (complete charge separation to give the separated radical/ion pair, charge recombination (BET), ISC to a triplet exciplex, dissipation of energy as radiationless decay to S_0, or even proton transfer from the secondary amine to give a radical pair). Work is in progress to obtain a more complete picture of the energetics and dynamics of these and other macrocycles.

4. Experimental section

4.1. Materials and methods

All commercially available reagents (Aldrich or Fluka) were used without further purification. 1,4-Bis(bromomethyl)-naphthalene was prepared as previously described.[28] Solvents for reactions were distilled over an adequate drying agent. Dichloromethane for fluorescence measurements was distilled over CaH_2 prior to use.

NMR spectra were recorded on a Varian INOVA 500 spectrometer (500 MHz for ^{1}H and 125 MHz for ^{13}C). Chemical shifts are reported in parts per million using residual undeuterated solvent peaks as internal standards. Mass spectra (ESI) were recorded on a Micromass Quattro LC spectrometer equipped with an electrospray ionization source and a triple-quadrupole analyzer. High resolution mass spectra (HRMS) were recorded in a VG Autospect (electron impact mode, EI^+) at the *Universitat de València*. Infrared spectra were recorded in a Perkin–Elmer 2000 FTIR spectrometer. UV–vis absorption spectra were recorded in a Hewlett-Packard 8453 apparatus. Steady-state fluorescence spectra were acquired in a Spex Fluorolog 3–11 equipped with a 450 W xenon lamp. Emission spectra were obtained from air equilibrated dichloromethane samples (ca. 1.3×10^{-4} M), exciting at 300 nm (280 nm for 4), in *right angle* mode and using 1×1 cm [3 mL] quartz cells. The curves were processed with the appropriate correction files. Excitation spectra were also recorded in order to assure that no impurities were responsible for the emission at longer wavelengths, i.e., the emitting LES and CTS are coming from the same singlet excited state. All measurements were done at 295 K otherwise stated.

4.2. Syntheses

4.2.1. General. The synthesis of the macrocyclic naphthalenophanes **1a–c** and **2a–c** was performed by the general method previously described.[9] The six open-chain peptidomimetic precursors **10a–c** and **11a–c** (Cbz-L-Val and Cbz-L-Phe combined with 1,*n*-alkanediamines [*n*=2, 3, and 4]) were obtained in multigram scale and their spectral properties matched those described.[9] Reaction of such precursors with 1,4-bis(bromomethyl)naphthalene (**12**) is described in detail for macrocycle **1a**. For the remaining macrocycles an identical procedure was employed. For the open-chain compounds **3** and **4** the synthesis was accomplished by means of *n*-propylamine instead of 1,*n*-alkanediamine.

4.2.1.1. Synthesis of compound 1a. Compound **10a** (0.750 g, 2.90 mmol), anhydrous K_2CO_3 (4.00 g, 29.00 mmol), tetrabutylammonium bromide (0.46 g, 1.45 mmol), and 1,4-bis(bromomethyl)naphthalene (0.91 g, 2.90 mmol) were placed in a flask containing dry CH_3CN (300 mL) and the mixture was refluxed for 12 h under a nitrogen atmosphere. The reaction was filtered (hot) and the solvent evaporated under reduced pressure. The crude product was dissolved in $CHCl_3$ (50 mL) and extracted with aqueous NaOH 0.01 M (50 mL, 3×). The organic phase was dried over anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure. The product was purified by silica flash chromatography using MeOH/CH_2Cl_2 (1:40) as the eluent to give 238 mg of **1a** as a white solid. Yield 20%; mp=202–203 °C. $[\alpha]_D^{20}$ +89.9 (*c* 0.01, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.73 (d, 6H, *J*=7.0 Hz), 0.97 (d, 3H, *J*=7.0 Hz), 1.01 (3H, *J*=7.0 Hz), 2.13 (m, 1H), 2.27 (m, 2H), 2.37 (m, 1H), 2.93 (d, 1H, *J*=4.0 Hz), 2.97 (m, 2H), 3.02 (d, 1H, *J*=4.0 Hz), 3.58 (d, 1H, *J*=13.5 Hz), 4.20 (d, 1H, *J*=14.0 Hz), 4.30 (d, 1H, *J*=14.0 Hz), 4.91 (d, 1H, *J*=13.5 Hz), 7.23 (d, 1H, *J*=7.0 Hz), 7.31 (d, 1H, *J*=7.0 Hz), 7.50 (m, 1H), 7.52 (m, 1H), 8.13 (m, 1H), 8.17 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.0, 17.3, 20.0, 31.6, 39.0, 39.1, 50.5, 53.9, 68.7, 70.2, 124.4, 126.5, 127.5, 131.7, 132.8, 135.0, 138.4, 174.4, 175.5; FTIR (KBr) 3263, 2965, 1638, 1528 cm^{-1}; UV–vis (CH_2Cl_2) (λ_{max}, ε) 291 nm, 6512 M^{-1} cm^{-1}; ESIMS *m*/*z*=411.7 ($M+H^+$), 433.6 ($M+Na^+$), 449.6 ($M+K^+$); HRMSEI$^+$ *m*/*z* calcd for $C_{24}H_{34}N_4O_2$ (M^+) 410.268177, found 410.268105.

4.2.1.2. Synthesis of 1b. Yield 690 mg, 40%. Spectroscopic data coincided with those previously reported.[11b]

4.2.1.3. Synthesis of 1c. Yield 210 mg, 41%; white solid; mp=241–243 °C. $[\alpha]_D^{20}$ +88.7 (*c* 0.01, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.37 (m, 2H), 0.56 (m, 2H), 0.90 (d, 6H, *J*=6.8 Hz), 1.12 (d, 6H, *J*=7.0 Hz), 1.90 (s, 2H), 2.28

(m, 2H), 3.20 (m, 2H), 3.80 (d, 2H, J=14.8 Hz), 4.70 (d, 2H, J=14.7 Hz), 6.84 (br s, 2H), 7.41 (s, 2H), 7.56 (m, 2H), 8.11 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.6, 20.1, 26.0, 31.3, 38.4, 52.0, 70.1, 124.7, 125.4, 126.4, 132.0, 136.3, 173.6; FTIR (KBr) 3373, 2958, 1671, 1509 cm^{-1}; UV–vis (CH_2Cl_2) (λ_{max}, ε) 288 nm, 7715 M^{-1} cm^{-1}; ESIMS m/z= 461.6 (M+Na$^+$); HRMSEI$^+$ m/z calcd for $C_{26}H_{38}N_4O_2$ (M$^+$) 438.299477, found 438.299698.

4.2.1.4. Synthesis of 2a. Yield 280 mg, 20%; mp=110–113 °C. $[\alpha]_D^{20}$ +77.9 (c 0.01, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.11 (m, 2H), 2.18 (br s, 2H), 2.36 (m, 1H), 2.57 (m, 1H), 2.67 (m, 1H), 3.04 (m, 2H), 3.28 (m, 2H), 3.38 (m, 1H), 3.40 (d, 1H, J=14.0 Hz), 3.57 (dd, 1H, J=10.5, 4.0 Hz), 4.03 (d, 1H, J=14.5 Hz), 4.12 (d, 1H, J= 14.5 Hz), 4.71 (d, 1H, J=14.0 Hz), 6.07 (br s, 1H), 6.15 (br s, 1H), 7.27–7.39 (m, 12H), 7.56 (m, 2H), 8.10 (d, 1H, J=9 Hz), 8.17 (d, 1H, J=9.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 38.8, 39.1, 39.9, 40.2, 49.7, 53.3, 64.8, 66.2, 124.1, 124.3, 126.3, 126.4, 126.9, 127.0, 127.4, 127.5, 128.8, 128.9, 129.0, 129.1, 131.4, 132.5, 134.4, 137.7, 137.8, 138.4, 174.3, 174.9; FTIR (KBr) 3369, 3050, 1654, 1517 cm^{-1}; UV–vis (CH_2Cl_2) (λ_{max}, ε) 290 nm, 7278 M^{-1} cm^{-1}; ESIMS m/z=507.4 (M+H$^+$), 529.4 (M+Na$^+$); HRMSEI$^+$ m/z calcd for $C_{32}H_{34}N_4O_2$ (M$^+$) 506.268177, found 506.268860.

4.2.1.5. Synthesis of 2b. Yield 509 mg, 35%; mp=74–79 °C. $[\alpha]_D^{20}$ −11.8 (c 0.01, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$, 328 K) δ 2.24 (m, 2H), 2.53 (m, 2H), 2.65 (m, 4H), 2.77 (m, 2H), 3.22 (dd, 2H, J=14.1, 4.4 Hz), 3.56 (br s, 2H), 3.80 (br s, 2H), 4.41 (m, 2H), 6.40 (br s, 2H), 7.21 (t, 2H, J=7.0 Hz), 7.25 (d, 4H, J=7.0 Hz), 7.26 (s, 2H), 7.30 (t, 4H, J=7.0 Hz), 7.35 (m, 2H), 8.00 (br s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.6, 29.4, 35.9, 39.0, 65.1, 124.3, 125.8, 126.5, 128.4, 129.1, 132.4, 138.1, 175.0; FTIR (KBr) 3339, 2935, 1651, 1520 cm^{-1}; UV–vis (CH_2Cl_2) (λ_{max}, ε) 290 nm, 7496 M^{-1} cm^{-1}; ESIMS m/z= 521.6 (M+H$^+$), 543.6 (M+Na$^+$); HRMSEI$^+$ m/z calcd for $C_{33}H_{36}N_4O_2$ (M$^+$) 520.283827, found 520.281919.

4.2.1.6. Synthesis of 2c. Yield 365 mg, 32%; mp=71–75 °C. $[\alpha]_D^{20}$ −11.9 (c 0.01, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.41 (m, 2H), 0.61 (m, 2H), 1.97 (br s, 2H), 2.28 (m, 2H), 2.64 (d, 1H, J=10.5 Hz), 2.67 (d, 1H, J=10.5 Hz), 3.24 (dd, 2H, J=14.1, 10.5 Hz), 3.39 (dd, 2H, J=14.0, 3.5 Hz), 3.60 (dd, 2H, J=14.0, 3.5 Hz), 3.65 (d, 2H, J=15.0 Hz), 4.46 (d, 2H, J=15.0 Hz), 6.82 (br s, 2H), 7.29–7.46 (m, 12H), 7.53 (m, 2H), 7.95 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.0, 29.8, 38.6, 40.0, 51.2, 53.6, 65.8, 124.1, 126.5, 127.4, 129.2, 129.3, 131.8, 137.8, 177.2; FTIR (KBr) 3349, 2927, 1651, 1656 cm^{-1}; UV–vis (CH_2Cl_2) (λ_{max}, ε) 289 nm, 7307 M^{-1} cm^{-1}; ESIMS m/z= 535.6 (M+H$^+$), 557.6 (M+Na$^+$); HRMSEI$^+$ m/z calcd for $C_{34}H_{38}N_4O_2$ (M$^+$) 534.299477, found 534.298988.

4.2.1.7. Synthesis of 14. The *N*-hydroxysuccinimide ester of N-Cbz-L-valine (5.00 g, 14.35 mmol) was dissolved in anhydrous THF (40 mL) cooled in an ice bath. *n*-Propylamine (1.20 mL, 14.35 mmol) dissolved in dry THF (10 mL) was added in several stages. The reaction mixture was refluxed for 4 h and then the solvent was evaporated at reduced pressure. The white solid was washed with cold water and dried in vacuum for 20 h at 65 °C. Yield of **14**: 3.98 g, 95%; mp=155–156 °C; ^{1}H NMR (500 MHz, d_6-DMSO) δ 0.84 (m, 9H), 1.39 (m, 2H), 1.92 (m, 1H), 2.97 (m, 1H), 3.06 (m, 1H), 3.79 (t, 1H, J=8.0 Hz), 5.02 (s, 2H), 7.18 (d, 1H, J= 8.9 Hz), 7.32 (m, 4H), 7.87 (s, 1H); ^{13}C NMR (125 MHz, d_6-DMSO) δ 11.2, 18.1, 19.1, 22.1, 30.1, 40.1, 60.2, 65.2, 127.5, 127.6, 128.2, 137.0, 155.9, 170.8; FTIR (KBr) 3300, 2962, 1686, 1642 cm^{-1}; ESIMS m/z=315.3 (M+Na$^+$), 331.2 (M+K$^+$).

4.2.1.8. Synthesis of 15. Product **14** (2.20 g, 7.52 mmol) was added to 15 mL of HBr/AcOH (33%) and the mixture was stirred at room temperature until CO_2 evolution ceased. To the resulting mixture 50 mL of distilled water was added and then extracted with chloroform (50 mL, 3×). Solid NaOH was then added up to a pH value of 12 and the resulting solution was saturated with NaCl and extracted with dichloromethane (50 mL, 3×). The organic phase was dried over $MgSO_4$ and evaporated under vacuum to obtain the desired product **15** (oil). Yield 1.07 g, 90%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.77 (d, 3H, J=6.5 Hz), 0.87 (t, 3H, J=8.5 Hz), 0.92 (d, 3H, J=7.5 Hz), 1.34 (br s, 2H), 1.47 (m, 2H), 2.22 (m, 1H), 3.16 (m, 3H), 7.28 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.4, 16.1, 19.7, 23.0, 30.9, 40.7, 60.3, 174.3; FTIR (NaCl) 3304, 2962, 1649, 1528 cm^{-1}; ESIMS m/z=181.2 (M+Na$^+$), 192.2 (M+K$^+$).

4.2.1.9. Synthesis of 3. Analogously to the synthesis of cyclophanes, coupling between **15** and 1,4-bis(bromomethyl)naphthalene (**12**) gave **3** (white solid). Yield 730 mg, 47%; mp=158–160 °C. $[\alpha]_D^{20}$ −9.9 (c 0.01, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86–0.88 (m, 12H), 0.97 (d, 6H, J=6.9 Hz), 1.41 (m, 4H), 1.66 (br s, 2H), 2.15 (m, 2H), 3.05 (m, 4H), 3.18 (m, 2H), 4.16 (s, 4H), 7.16 (m, 2H), 7.38 (s, 2H), 7.57 (m, 2H), 8.14 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.5, 17.7, 19.7, 22.9, 31.4, 40.6, 51.6, 68.5, 124.3, 126.1, 126.2, 132.1, 135.3, 173.4; FTIR (KBr) 3308, 2961, 1641, 1556 cm^{-1}; UV–vis (CH_2Cl_2) (λ_{max}, ε) 288 nm, 7644 M^{-1} cm^{-1}; ESIMS m/z=469.4 (M+H$^+$), 491.3 (M+Na$^+$); HRMSEI$^+$ m/z calcd for $C_{28}H_{43}N_4O_2$ ((M−1)$^+$) 467.338602, found 467.338524.

4.2.1.10. Synthesis of 4. Analogously to the synthesis of cyclophanes, coupling between **15** and 1-(chloromethyl)-naphthalene (**16**) gave **4** (white solid). Yield 184 mg, 55%; mp=80–81 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (d, 3H, J=7.0 Hz), 0.88 (t, 3H, J=6.0 Hz), 0.96 (d, 3H, J=7.0 Hz), 1.42 (m, 2H), 2.19 (m, 1H), 3.10 (m, 2H), 3.19 (m, 1H), 4.20 (s, 2H), 7.24 (br s, 1H), 7.44 (m, 1H), 7.51 (m, 1H), 7.55 (m, 1H), 7.81 (m, 2H), 7.88 (d, 1H, J=8.0 Hz), 8.08 (d, 1H, J=8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.4, 17.8, 19.5, 22.9, 31.2, 40.6, 51.4, 68.4, 123.2, 125.5, 125.8, 126.4, 128.3, 129.0, 131.6, 133.9, 170.0; FTIR (KBr) 3290, 2960, 1637, 1555 cm^{-1}; UV–vis (CH_2Cl_2) (λ_{max}, ε) 282 nm, 6449 M^{-1} cm^{-1}; ESIMS m/z= 299.3 (M+H$^+$), 321.3 (M+Na$^+$); HRMSEI$^+$ m/z calcd for $C_{19}H_{26}N_2O$ (M$^+$) 298.204514, found 298.203308.

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