Cycloaddition to an anthracene-derived macrocyclic receptor with supramolecular control of regioselectivity†

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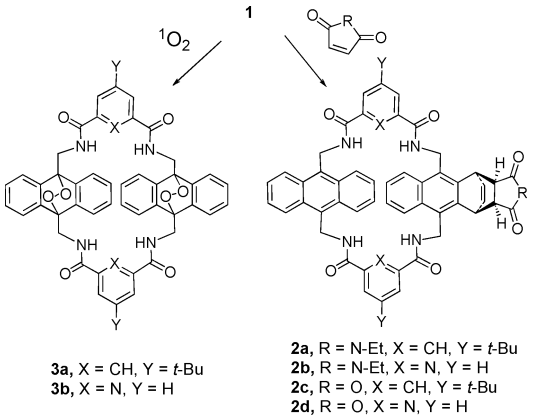
***N*-Ethylmaleimide and maleic anhydride add to the interior face of one anthracene wall with unusual 1,4-regioselectivity, whereas singlet oxygen adds to both anthracene walls with 9,10-regioselectivity.**

Recently, we described the preparation of anthracene-containing macrocyclic tetralactams **1a** and **1b** and showed that they can encapsulate squaraine dyes with high affinity in a range of solvent systems, including the interior of living cells.[1] The expanding literature on anthracene-containing receptors suggests that members of the compound family **1** may be versatile structural components in various supramolecular devices such as fluorescent sensors, shuttles, and solid-state photonic materials.[2] Anthracene derivatives are also known to undergo cycloaddition reactions, often in a reversible manner, and these covalent processes have been investigated as switching mechanisms for molecular machines.[3] This knowledge has prompted us to conduct a systematic study of the chemical, photophysical, and molecular recognition properties of receptor family **1**. Here we report our first results on the propensity to undergo cycloaddition reactions. We find that macrocycles **1a** and **1b** can react in very high yield with the archetype dienophiles, *N*-ethylmaleimide, maleic anhydride, and singlet oxygen. Furthermore, we provide evidence indicating that the cycloaddition regioselectivity can be controlled by non-covalent interactions within a pre-reaction complex.

Shown in Fig. 1 is the X-ray crystal structure‡ of **1a** with an included molecule of ethyl acetate. All four NH residues of the tetralactam are directed into the macrocycle cavity, two are engaged in bifurcated hydrogen bonds with the ethyl acetate carbonyl oxygen, whereas the other NH pair form hydrogen bonds with a second ethyl acetate outside the cavity. The two anthrylene chromophores adopt a near-parallel orientation; this preorganized conformation helps explain why **1a** and **1b** are quite soluble in weakly polar organic solvents (in contrast to the extreme insolubility of the Leigh-type phenylene analogues[4]) and why the solution-state fluorescence spectra do not exhibit excimer bands in a range of solvents of different polarities.[1]

The first reactions to be discussed are cycloadditions of **1a** and **1b** with *N*-ethylmaleimide and maleic anhydride to give



Scheme 1 Synthesis of cycloadduct families **2** and **3**.

the monoadducts **2a–d** (Scheme 1). Focusing on the reaction of **1a** with *N*-ethylmaleimide as an illustrative example, we find that heating a 1 : 1 mixture in chloroform at 50 °C for 24 h gives **2a** in quantitative yield.§ The same result was also obtained in solid-state reaction, where the solvent was removed and the residue heated at 40 °C. The structure of

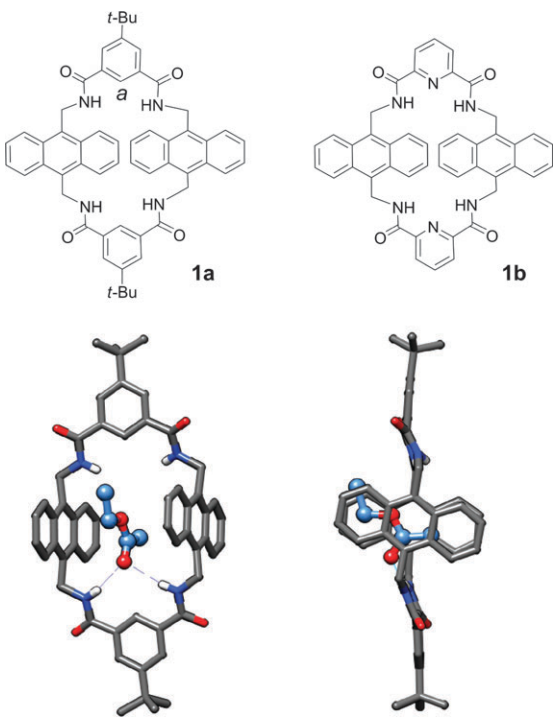


Fig. 1 Two views of the X-ray structure of **1a**·ethyl acetate.

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† Electronic supplementary information (ESI) available: Synthesis and spectral data, computational methods, and crystallographic details. CCDC 717859 (**1a**) and 717858 (**3b**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b901814j

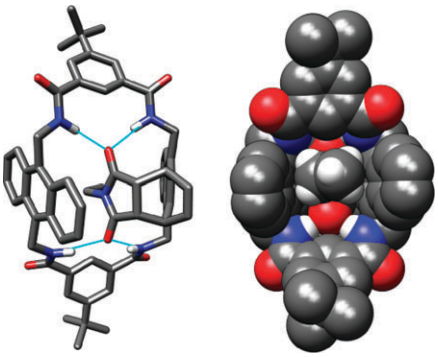

Fig. 2 NMR-derived structure of **2a**, (left) stick model highlighting intramolecular hydrogen bonding, (right) space-filling model highlighting the *N*-ethyl group inside the macrocyclic cavity.

2a, elucidated by a combination of multidimensional NMR and computer modeling,[5] displays two noteworthy stereochemical features: (a) the maleimide adds with 1,4-regioselectivity to one of the two anthracenes, and (b) it forms exclusively the *endo*-isomer, with intramolecular hydrogen bonding to the four tetralactam NH residues, placing the *N*-ethyl group against the aromatic cavity walls (Fig. 2). The 1,4-addition regioselectivity is unusual because Diels–Alder reactions with anthracene derivatives usually produce the 9,10-isomer.[6] For example, the addition of *N*-methylmaleimide to 9,10-dimethylanthracene forms the 9,10-adduct in 95% yield.[7] To explain this altered reactivity, we employed NMR spectroscopy to study the ground-state supramolecular interaction of *N*-ethylmaleimide and **1a**.[8] Addition of one molar equivalent of *N*-ethylmaleimide to a solution of **1a** produced changes in ^{1}H NMR chemical shifts that were diagnostic for rapid and reversible inclusion of the maleimide inside the macrocycle. For example, there were large downfield migrations of the NH signals and proton *a* in **1a** (and even greater changes when the complex reacted to form product **2a**, see Fig. 3). Moreover, the signals corresponding to the maleimide *N*-ethyl group were strongly shielded by the anthracene sidewalls. Computer modeling of the pre-reaction complex[5] suggested the hydrogen bonded structure shown in Fig. 4, with the reactive dienophile double bond located cofacially over the anthrylene 1,4-carbons.¶ Consistent with this reaction model is the monoadduct **2b** which was produced in 90% isolated yield by reacting *N*-ethylmaleimide with

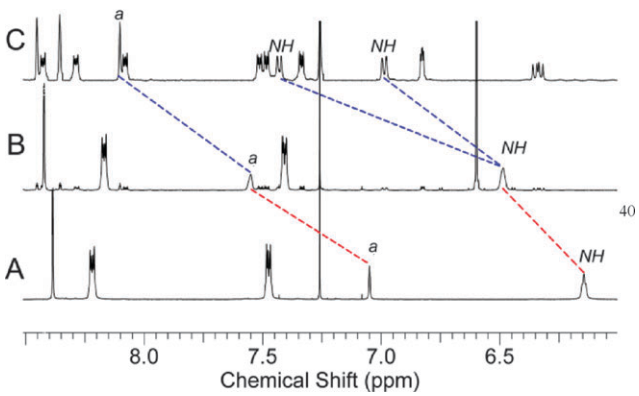

Fig. 3 Partial ^{1}H NMR spectra ($CDCl_3$) of (A) **1a**, (B) inclusion complex of *N*-ethylmaleimide and **1a**, (C) **2a**.

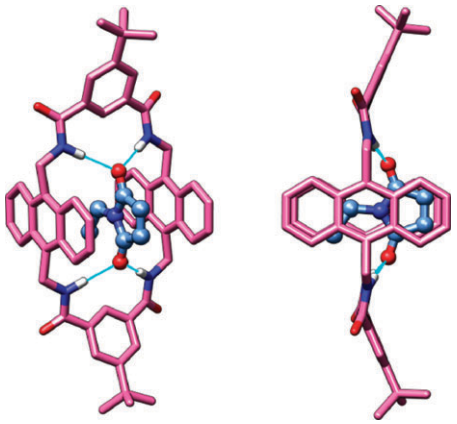

Fig. 4 Two views of the computed structure for the **1a**·*N*-ethylmaleimide inclusion complex.

homologous macrocycle **1b**. Furthermore, the related 1,4-addition products, **2c** and **2d**, were obtained in 70% yield when macrocycles **1a** and **1b** were reacted with equimolar amounts of maleic anhydride. The decreased yields for these latter reactions are attributed to lower amounts of pre-reaction complex since the maleic anhydride carbonyls are weaker hydrogen bond acceptors.[9] Taken together, the evidence strongly suggests that the unusual 1,4-regioselectivity is due to supramolecular control, a phenomenon that has been demonstrated with a few other Diels–Alder reaction systems.[10]

The second reaction set to be discussed is cycloaddition with singlet oxygen.[11] Compounds **1a** and **1b** can be stored as solids for months on the benchtop with no measurable decomposition. Upon irradiation in the absence of oxygen they form intractable mixtures with broad NMR lines (*i.e.*, they do not undergo clean homodimerization). However, they both react rapidly in solution with excess singlet oxygen that has been formed by triplet photosensitization. For example, irradiation of an oxygen saturated solution of **1a** or **1b** in the presence of 1% methylene blue produced the corresponding bis-*endo*-peroxides **3a** and **3b** in quantitative yield. These bis-*endo*-peroxides were stable to storage at room temperature and underwent decomposition upon heating at 120 °C for extended periods (cycloreversion was not observed). The molecular structures were elucidated by a combination of standard spectrometric methods and, for **3b**, single-crystal X-ray diffraction. The solid-state structure of **3b** confirms the 9,10-addition regioselectivity to both anthrylene units (Fig. 5). There is also a bridging water molecule between one pair of macrocycle NH residues, whereas the other NH pair

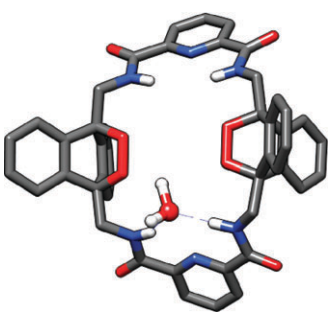

Fig. 5 X-Ray structure of **3b** with a molecule of water.

forms bifurcated hydrogen bonds to a proximal macrocyclic amide oxygen. The macrocycle adopts a boat conformation in the solid-state, implying inequivalent shielding at each end of the anthrylene units, but in solution this conformation must be in rapid exchange with its degenerate isomer, since the ^{1}H NMR spectrum exhibits a symmetrical pattern with sharp lines, even at low temperature. The location of both *endo*-peroxide groups inside the macrocyclic cavity suggests to us that the reactive singlet oxygen molecules were delivered to the internal faces of the anthrylene chromophores, but we cannot completely rule out the less likely possibility of external addition followed by bond rotation and conformational exchange.

In summary we report that macrocyclic receptor family **1** with two cofacial anthrylene chromophores can undergo quantitative cycloaddition reactions under mild conditions. The reaction regioselectivity depends on the size and supramolecular complementarity of the dienophile. The unusual 1,4-addition of *N*-ethylmaleimide and maleic anhydride to only one of the anthrylene walls is attributed to formation of a non-covalent, pre-reaction complex that promotes cycloaddition inside the macrocyclic cavity. In contrast, the smaller dienophile, singlet oxygen, adds to both anthrylene walls with 9,10-addition selectivity.

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Notes and references

‡ Crystal data for **1a**: $C_{65}H_{69}Cl_3N_4O_8$, M_r = 1140.59, triclinic, space group $P\bar{1}$, a = 12.5937(5) Å, b = 13.2158(5) Å, c = 18.7174(8) Å, α = 73.655(2)°, β = 88.986(2)°, γ = 79.997(2)°, V = 2942.3(2) Å^3, D_{calc} = 1.287 mg m^{-3}, T = 100(2) K, Z = 2, 44 027 reflections measured and 10 733 were independent (R_{int} = 0.0465), R_1 = 0.0649 [$I > 2\sigma(I)$], wR_2 = 0.1952 (all data). GOF = 1.091. Crystal data for **3b**: $C_{50}H_{42}Cl_{12}N_6O_9$, M_r = 1296.30, monoclinic, space group $P2_1/c$, a = 17.4237(13) Å, b = 18.9917(14) Å, c = 17.0898(12) Å, α = 90°, β = 102.159(3)°, γ = 90°, V = 5528.2(7) Å^3, D_{calc} = 1.557 mg m^{-3}, T = 100(2) K, Z = 4, 78 882 reflections measured and 7318 were independent (R_{int} = 0.1208), R_1 = 0.0649 [$I > 2\sigma(I)$], wR_2 = 0.1908 (all data). GOF = 1.084. The crystal size was very small and diffraction data at high angles are very weak or absent resulting in a higher R_{int} for redundant data.

§ A room temperature reaction of macrocycle **1a** or **1b** with a fifty-fold excess of *N*-ethylmaleimide produced only the corresponding monoadducts **2a** or **2b**, respectively. There was no evidence for addition of a second molar equivalent of *N*-ethylmaleimide to the other anthrylene unit.

¶ Adding 20% DMSO to the reaction of **1a** and *N*-ethylmaleimide in chloroform greatly slowed the reaction rate, presumably because it inhibited formation of the pre-reaction complex.

1 (*a*) J. J. Gassensmith, E. Arunkumar, L. Barr, J. M. Baumes, K. M. DiVittorio, J. R. Johnson, B. C. Noll and B. D. Smith, *J. Am. Chem. Soc.*, 2007, **129**, 15054–15059; (*b*) J. J. Gassensmith, L. Barr, J. M. Baumes, A. Paek, A. Nguyen and B. D. Smith, *Org. Lett.*, 2008, **10**, 3343–3346.

2 (*a*) K. Hirose, Y. Shiba, K. Ishibashi, Y. Doi and Y. Tobe, *Chem.–Eur. J.*, 2008, **14**, 981–986; (*b*) A. J. Wilson, J. Hong, S. Fletcher and A. D. Hamilton, *Org. Biomol. Chem.*, 2007, **5**, 276–285; (*c*) Y. Zou, D. D. Young, A. Cruz-Montanez and A. Deiters, *Org. Lett.*, 2008, **10**, 4661–4664; (*d*) B. Lohse, R. Vestberg, M. T. Ivanov, S. R Hvilsted, R. H. Berg, C. J. Hawker and P. S. Ramanujam, *Chem. Mater.*, 2008, **20**, 6715–6720; (*e*) K. Hirose, Y. Shiba, K. Ishibashi, Y. Doi and Y. Tobe, *Chem.–Eur. J.*, 2008, **14**, 981–986; (*f*) L. Fabbrizzi, M. Licchelli, A. Perotti, A. Poggi, G. Rabaioli, D. Sacchi and A. Taglietti, *J. Chem. Soc., Perkin Trans. 2*, 2001, 2108–2113; (*g*) A. Granzhan and M.-P. Teulade-Fichou, *Chem.–Eur. J.*, 2009, **15**, 1314–1318; (*h*) P. P. Neelakandan and D. Ramaiah, *Angew. Chem., Int. Ed.*, 2008, **47**, 8407–8411; (*i*) D. C. Magri, G. J. Brown, G. D. McClean and A. P. de Silva, *J. Am. Chem. Soc.*, 2006, **128**, 4950–4951.

3 (*a*) J.-B. Lin, X.-N. Xu, X.-K. Jiang and Z.-T. Li, *J. Org. Chem.*, 2008, **73**, 9403–9410; (*b*) B. Masci, S. Pasquale and P. Thuery, *Org. Lett.*, 2008, **10**, 4835–4838; (*c*) S. J. Rowan, S. J. Cantrill, G. R. L. Cousins, J. K. M. Sanders and J. F. Stoddart, *Angew. Chem., Int. Ed.*, 2002, **41**, 898–952; (*d*) D. Zehm, W. Fudickar and T. Linker, *Angew. Chem., Int. Ed.*, 2007, **46**, 7689–7692; (*e*) W. Fudickar and T. Linker, *Chem. Commun.*, 2008, 1771–1773.

4 (*a*) A. G. Johnston, D. A. Leigh, A. Murphy, J. P. Smart and M. D. Deegan, *J. Am. Chem. Soc.*, 1996, **118**, 10662–10663; (*b*) Y. Inoue, T. Kanbara and T. Yamamoto, *Tetrahedron Lett.*, 2003, **44**, 5167–5169.

5 Computer modeling used molecular mechanics and the OPLS_2005 force field in MacroModel, in *Maestro*, version 8.0, Schrödinger, LLC, New York, NY, 2005.

6 (*a*) Y. Chung, B. F. Duerr, T. A. McKelvey, P. Nanjappan and A. W. Czarnik, *J. Org. Chem.*, 1989, **54**, 1018–1032; (*b*) J. C. C. Atherton and S. Jones, *Tetrahedron*, 2003, **59**, 9039–9057; (*c*) C. Kitamura, M. Hasegawa, H. Ishikawa, J. Fujimoto, M. Ouchi and A. Yoneda, *Bull. Chem. Soc. Jpn.*, 2004, **77**, 1385–1393.

7 W. K. Anderson and A. S. Milowsky, *J. Org. Chem.*, 1985, **50**, 5423–5424.

8 At room temperature the cycloaddition reaction was slow enough to allow NMR studies of the pre-reaction complex; however, an association constant could not be measured by titration methods because of interfering product formation at the higher concentrations.

9 A. M. Rijs, I. Compagnon, J. Oomens, J. S. Hannam, D. A. Leigh and W. J. Buma, *J. Am. Chem. Soc.*, 2009, **131**, 2428–2429.

10 (*a*) M. Yoshizawa, M. Tamura and M. Fujita, *Science*, 2006, **312**, 251–254; (*b*) G. Mehta, R. Uma, M. N. Jagadeesh and J. Chandrasekhar, *Chem. Commun.*, 1998, 1813–1814.

11 (*a*) J.-M. Aubry, C. Pierlot, J. Rigaudy and R. Schmidt, *Acc. Chem. Res.*, 2003, **36**, 668–675; (*b*) A. R. Reddy and M. Bendikov, *Chem. Commun.*, 2006, 1179–1181.