



Cite this: *Chem. Commun.*, 2016, 52, 1032

Received 3rd November 2015,
Accepted 18th November 2015

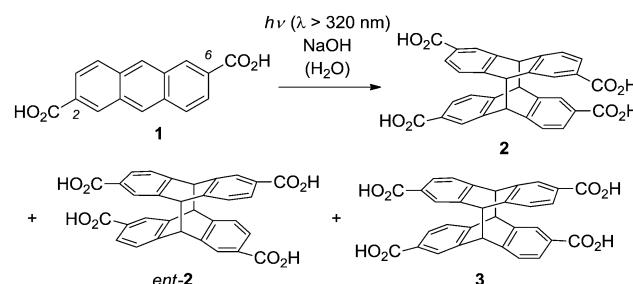
DOI: 10.1039/c5cc09107a

www.rsc.org/chemcomm

A chiral template was constructed from 7-ethynyl-1,5,7-trimethyl-3-azabicyclo[3.3.1]nonan-2-one by Sonogashira cross-coupling with 4,4''-diiodoterphenyl and was shown to bind the title compound strongly by hydrogen bonding resulting in enantioselectivities of up to 55% enantiomeric excess (ee) in the [4+4] anthracene photodimerization.

Irradiation of anthracene-2,6-dicarboxylic acid (**1**) in an aqueous basic solution leads to the formation of two diastereomeric [4+4] photodimerization¹ products *rac*-**2** and **3** (Scheme 1).² The so-called *anti* diastereoisomer *rac*-**2** is chiral and its two antipodes **2** and *ent*-**2**³ are formed in the absence of a chiral control element in a 1:1 ratio, *i.e.* as a racemic mixture. Compound **3** is an achiral *meso*-compound. In contrast to the enantioselective [4+4] photodimerization of anthracene-2-carboxylic acid, which has been extensively studied in recent years,⁴ there have been relatively few investigations on the photodimerization of **1**. In a fundamental circular dichroism (CD) study, the absolute configuration of compounds **2** and *ent*-**2** was determined, which allows their unambiguous assignment based on their chiroptical data, *e.g.* the specific rotation.^{2,3}

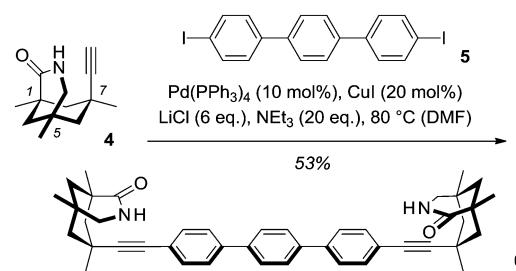
We became interested in the [4+4] photodimerization of diacid **1**, because its two carboxylic acid groups seemed ideally positioned for a possible templation by a chiral difunctional hydrogen-bonding device. While chiral lactams with a 1,5,7-trimethyl-3-azabicyclo[3.3.1]nonan-2-one skeleton have amply shown their potential as templates for enantioselective photochemical reactions,^{5,6} their use is limited to nonpolar solvents such as toluene, in which the two hydrogen bonds between substrate and template are sufficiently strong⁷ to exert the desired



Scheme 1 Products **2**, *ent*-**2**, and **3** obtained by [4+4] photodimerization of anthracene-2,6-dicarboxylic acid (**1**) in an achiral environment.

directing effect. It was anticipated that dicarboxylic acid **1**⁸ would be capable of forming four hydrogen bonds to an appropriately designed chiral template with two chemically linked lactam units of identical chirality. A template of this type was readily constructed by Sonogashira cross-coupling of known 7-ethynyl-1,5,7-trimethyl-3-azabicyclo[3.3.1]nonan-2-one (**4**)⁹ with commercially available 4,4''-diiodoterphenyl (**5**). Due to the low solubility of terphenyl **5** in nonpolar solvents, the use of DMF as the solvent was required for a successful transformation. In other solvents, *e.g.* THF, exclusive alkyne dimerization was observed (Scheme 2).

Gratifyingly, the solubility of difunctional template **6** in organic solvents was sufficient to record its UV-Vis and fluorescence



Scheme 2 Synthesis of chelating, *C*₂-symmetric chiral template **6** by Sonogashira cross-coupling of 4,4''-diiodoterphenyl (**5**) and alkyne **4**.

^a Department Chemie and Catalysis Research Center (CRC), Technische Universität München, 85747 Garching, Germany. E-mail: thorsten.bach@ch.tum.de; Fax: +49 89 28913315; Tel: +49 89 28913330

^b Department of Applied Chemistry, Osaka University, 2-1 Yamada-oka, Suita 565-0871, Japan. E-mail: inoue@chem.eng.osaka-u.ac.jp; Fax: +81-6-6879-7923; Tel: +81-6-6879-7920

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c5cc09107a



spectra. Its photophysical behaviour is dominated by the terphenyl chromophor¹⁰ and the spectra resemble the spectra of unsubstituted terphenyl (see ESI†). The singlet-state lifetime was determined by the single-photon counting method¹¹ as 0.7 ns. In order to study the complexation between dicarboxylic acid **1** and template **6**, fluorescence spectra of **1** were recorded with excitation at $\lambda_{\text{exc}} = 388$ nm (0–1' transition of the 1L_b band¹²). At this wavelength, template **6** is transparent and light absorption is exclusively due to acid **1**. Fluorescence spectra were measured at a fixed acid concentration of 4.95 μM in CH_2Cl_2 /DMSO (0.02% DMSO v/v) with varying concentrations of the template. Fluorescence quenching was observed upon gradual addition of the template. Appreciable peak shifts without any isoemissive points were detected, indicating that not a single but multiple complex species are formed in the system with a weak fluorescence at longer wavelength. Least-squares-fit analysis of the intensity changes assuming a 1:1 stoichiometry enabled us to determine the apparent association constant (K_a) for complex **1**–**6**.¹³ The fluorescence spectral changes at 25 °C are exemplified in Fig. 1. In an analogous fashion spectral changes were recorded at 15 °C and at 5 °C (see ESI†). As expected, the K_a values were relatively high and increased modestly by lowering the temperature; *i.e.* $(6.6 \pm 0.7) \times 10^5 \text{ M}^{-1}$ at 25 °C, $(1.5 \pm 0.4) \times 10^6 \text{ M}^{-1}$ at 15 °C, and $(2.3 \pm 0.7) \times 10^6 \text{ M}^{-1}$ at 5 °C. From the van't Hoff plot of the temperature-dependent K_a values obtained (see ESI†), we calculated the enthalpy and entropy changes for the 1:1 complexation of **1** with **6** as $\Delta H^\circ = -43 \pm 8 \text{ kJ mol}^{-1}$ and $T\Delta S^\circ = -9 \pm 8 \text{ kJ mol}^{-1}$ ($T = 298 \text{ K}$). The large enthalpic gain is likely to arise from the two sets of hydrogen-bonding interactions at both ends of dicarboxylic acid **1**, while the modest entropic loss is attributable to the complexation without accompanying extensive desolvation in less solvating dichloromethane.

Initial studies regarding an enantioselective [4+4] photodimerization were performed at an irradiation wavelength of $\lambda \geq 370$ nm in CH_2Cl_2 solution. The concentration of dicarboxylic acid **1** in solution was determined by UV-Vis spectroscopy after a given aliquot of the acid solution had been treated with a given amount of template **6**, sonicated, filtered and degassed (Table 1). It was anticipated that an efficient enantioface differentiation would operate given the high association constant of complex **1**–**6** and given the well established high degree of steric shielding

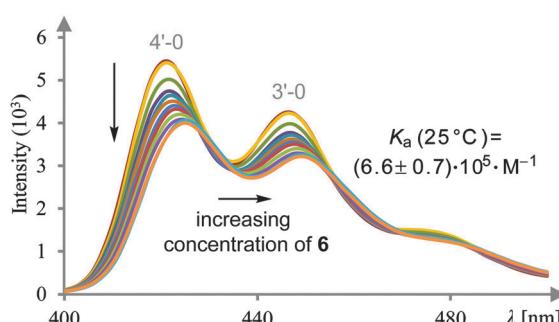


Fig. 1 Determination of the association constant K_a for complex **1**–**6** at 25 °C by fluorescence spectroscopic titration at $\lambda_{\text{exc}} = 388$ nm. $c(\mathbf{1}) = 4.95 \mu\text{M}$, $c(\mathbf{6}) = 0\text{--}24.6 \mu\text{M}$ in CH_2Cl_2 /DMSO (0.02% DMSO v/v).

Table 1 Enantioselective [4+4] photodimerization of dicarboxylic acid **1** in the presence of chiral template **6**

Entry ^a	$c(\mathbf{1})$ [μM]	$c(\mathbf{6})$ [mM]	T [°C]	t [h]	conv. ^b [%]	$\mathbf{2} + \text{ent-2}$	$\text{d.r.} = \frac{\mathbf{2} + \text{ent-2}}{\mathbf{3}}$	ee^c [%]
						$\mathbf{2} - \text{ent-2}$	$\text{ee} = \frac{\mathbf{2} - \text{ent-2}}{\mathbf{2} + \text{ent-2}}$	
1	9.3	0.04	25	5	8	53/47	<5	
2	176	1.0	0	1	7	57/43	13	
3	210	1.0	-25	2	13	69/31	29	
4	174	1.0	-50	4	10	76/24	55	

^a The reactions were performed at the indicated temperature in quartz cuvettes employing a high pressure mercury lamp as irradiation source and a UV 37 filter (50% transmission at $\lambda = 370$ nm). ^b Determined by UV-Vis spectroscopy. ^c Determined by HPLC analysis.

exerted by the 1,5,7-trimethyl-3-azabicyclo[3.3.1]nonan-2-one scaffold⁵ of the template. Unexpectedly, chiral HPLC analysis of the reaction mixture photoirradiated at 25 °C and at low substrate concentration showed the formation of essentially racemic cyclo-dimer **2** in addition to achiral **3** in comparable yields (entry 1). In a second experiment, the substrate concentration was increased and the reaction was performed at 0 °C (entry 2). A notable enantioselectivity was recorded and the major enantiomer was assigned to structure **2** on the basis of the known elution order for enantiomers **2** and *ent*-**2** on a previously reported chiral HPLC phase.² At lower temperatures, the enantioselectivity was significantly improved to give **2** in 29% enantiomeric excess (ee) at -25 °C (entry 3) and in a much higher 55% ee at -50 °C (entry 4).

DFT calculations¹⁴ revealed that the coordination mode of dicarboxylic acid **1** to template **6** is more complex (Fig. 2) than originally assumed based on simple molecular models. Apparently, there are two diastereomeric conformations **1**–**6**–**I** and **1**–**6**–**II**, which are formally interconvertable by a rotation around the anthracene–COOH single bond.¹⁵ In addition, it was shown that also the central phenyl ring of the terphenyl unit can rotate within complexes **I** and **II**¹⁶ which eventually leads to two pairs of conformers **I**/**I'** and **II**/**II'** for **1**–**6**. The energy difference between conformers **I** and **I'** or **II** and **II'** (Table 2) was found to be rather marginal ($<0.1 \text{ kJ mol}^{-1}$), while that between **I** and **II** or **I'** and **II'** was more significant ($0.2\text{--}0.3 \text{ kJ mol}^{-1}$) but still small (Table 2).

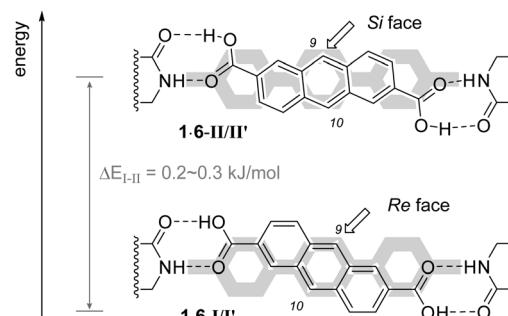


Fig. 2 Conformations **I**/**I'** and **II**/**II'** for complex **1**–**6** and shielding by the terphenyl unit (in gray). Note that two conformers are also possible in the terphenyl unit (see narrative).



Table 2 Calculated relative stability of the conformers **I/I'** and **II/II'** of complex **1-6** and calculated parameters for the 1st (1L_b) and 2nd (1L_a) electronic transitions of the respective complex^a

Complex	ΔE [kJ mol ⁻¹]	1st transition (1L_b band)		2nd transition (1L_a band)	
		Excitation energy [eV]	Oscillator strength	Excitation energy [eV]	Oscillator strength
I	≡ 0	3.429	0.0468	3.712	0.0216
I'	0.00	3.428	0.0468	3.708	0.0232
II	+0.20	3.445	0.0497	3.737	0.0185
II'	+0.28	3.446	0.0498	3.739	0.0179

^a The calculations were performed at the RI-CC2/def2-TZVP//DFT-D3(BJ)-TPSS/def2-TZVP level.^{14,17}

The fact that not a single but two pairs of conformations are located closely in energy enables facile switching of the enantio-topic face differentiation when going from **I/I'** to **II/II'**. While the terphenyl unit shields efficiently the Si face in conformation **I/I'** and attack at C9 should occur exclusively from the Re face, the opposite situation is encountered in conformation **II/II'** and Si face attack should be preferred. The lower energy of conformation **I/I'** vs. **II/II'** is in agreement with the preferred formation of enantiomer **2** in the [4+4] photodimerization at lower temperatures (Table 1), which is the result of a Re face attack. Antipodal *ent*-**2** is formed by a Si face attack of two dicarboxylic acids, both of which adopt the Si-face exposed conformation **II/II'**. The achiral product **3** is likely the product of a photodimerization in which the two dicarboxylic acids are in opposing chiral complexation environments, *i.e.* one in conformation **I/I'** and the other in conformation **II/II'**.

The energies of electronic transitions of the complexes were estimated at the RI-CC2/def2-TZVP level¹⁷ of theory (Table 2). Intriguingly, significant differences were found in the excitation energy of the 1L_b band (*ca.* 0.02 eV) between conformers **I/I'** and **II/II'**. Although the calculated excitation energies are slightly overestimated (relative to the experiment) due to a known systematic error,^{2,18} it is reasonable to assume that there is a notable difference in excitation wavelength for **I/I'** and **II/II'** at the lowest energy band. At a wavelength of $\lambda = 400$ nm the calculated value for the excitation energy of *ca.* 0.02 eV corresponds to a $\Delta\lambda$ of *ca.* 3 nm possibly enabling a selective excitation. To test this possibility, wavelength-selective irradiation experiments were performed employing adequate band-pass filters (Table 3). At $\lambda = 390$ nm, the enantioselectivity was expected to reflect the value previously recorded at room temperature. The fact that an ee was now notable (Table 3, entry 1) as opposed to entry 1 of Table 1 is ascribed to the higher concentration of the substrate in the latter experiment.

At $\lambda = 410$ nm (entry 2), there was a slight drop in enantioselectivity compared to $\lambda = 390$ nm (entry 1), which was, however, within the experimental error of ee determination by chiral HPLC. It was secured that there was no enantiomeric enrichment of *ent*-**2**, *i.e.* a negative ee. Pleasingly, irradiation at $\lambda = 420$ nm (entry 3) resulted in a significant enantioselectivity increase indicating that the enantioselectivity is wavelength dependent. In addition, due to the higher absorbance at this wavelength, the conversion of the reaction was increased compared to the

Table 3 Wavelength-dependent enantioselectivity in the [4+4] photodimerization of dicarboxylic acid **1** in the presence of chiral template **6**

Entry ^a	c (1) [μ M]	λ^a [nm]	conv. ^b [%]	d.r. ^c		ee ^c [%]
				59/41	7	
1	201	390	24	59/41	7	
2	207	410	26	61/39	6	
3	186	420	35	60/40	16	

^a The reactions were performed at 25 °C in quartz cuvettes employing a 300 W xenon lamp with an appropriate band-pass filter (full width at half maximum: ± 10 nm) for each indicated wavelength. ^b Determined by UV-Vis spectroscopy. ^c Determined by HPLC analysis.

entries 1 and 2. The latter results support the hypothesis, that the two conformations **I/I'** and **II/II'** show different UV/Vis absorption properties and that conformation **I/I'** can be selectively excited.

In summary, the first enantioselective [4+4] photodimerization of anthracene-2,6-dicarboxylic acid (**1**) has been achieved employing a new type of chiral scaffold. Despite significant enantioselectivities for product enantiomer **2** (up to 55% ee), it was found that the fixation within the scaffold is not completely rigid but rather allows for rotation of the photochemically active entity. An intriguing collateral finding resulted from DFT calculations, which indicated that the two diastereomeric complexes **I/I'** and **II/II'** absorb at different wavelengths. The enantioselectivity in favor of product **2** was shown to be wavelength dependent.

This project was supported by the Deutsche Forschungsgemeinschaft (GRK 1626, Chemical Photocatalysis) and by the Alexander von Humboldt foundation (Humboldt Research Award to Y. I.).

Notes and references

- Reviews: (a) S. M. Sieburth and N. T. Cunard, *Tetrahedron*, 1996, **52**, 6251–6282; (b) S. M. Sieburth, in *Synthetic Organic Photochemistry*, ed. A. G. Griesbeck and J. Mattay, Dekker, New York, 2005, vol. 12, pp. 239–268; (c) H. Meier and D. Cao, *Chem. Soc. Rev.*, 2013, **42**, 143–155.
- A. Wakai, H. Fukasawa, C. Yang, T. Mori and Y. Inoue, *J. Am. Chem. Soc.*, 2012, **134**, 4990–4997.
- Compound **2** has the (*M*)-configuration, while compound *ent*-**2** is (*P*)-configured.
- Examples: (a) Y. Kawanami, H. Tanaka, J.-i. Mizoguchi, N. Kanehisa, G. Fukuhara, M. Nishijima, T. Mori and Y. Inoue, *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.*, 2013, **69**, 1411–1413; (b) G. Fukuhara, T. Nakamura, Y. Kawanami, C. Yang, T. Mori, H. Hiramatsu, Y. Dan-oh, T. Nishimoto, K. Tsujimoto and Y. Inoue, *J. Org. Chem.*, 2013, **78**, 10996–11006; (c) M. Nishijima, H. Kato, C. Yang, G. Fukuhara, T. Mori, Y. Araki, T. Wada and Y. Inoue, *ChemCatChem*, 2013, **5**, 3237–3240; (d) Y. Kawanami, H. Umehara, J.-i. Mizoguchi, M. Nishijima, G. Fukuhara, C. Yang, T. Mori and Y. Inoue, *J. Org. Chem.*, 2013, **78**, 3073–3085; (e) M. Nishijima, M. Goto, M. Fujikawa, C. Yang, T. Mori, T. Wada and Y. Inoue, *Chem. Commun.*, 2014, **50**, 14082–14085; (f) J. Yao, Z. Yan, J. Ji, W. Wu, C. Yang, M. Nishijima, G. Fukuhara, T. Mori and Y. Inoue, *J. Am. Chem. Soc.*, 2014, **136**, 6916–6919.
- Examples (a) T. Bach, H. Bergmann and K. Harms, *Angew. Chem., Int. Ed.*, 2000, **39**, 2302–2304; (b) T. Bach, T. Aechtner and B. Neumüller, *Chem. – Eur. J.*, 2002, **8**, 2464–2475; (c) B. Grosch,



C. N. Orlebar, E. Herdtweck, M. Kaneda, T. Wada, Y. Inoue and T. Bach, *Chem. – Eur. J.*, 2004, **10**, 2179–2189; (d) P. Selig, E. Herdtweck and T. Bach, *Chem. – Eur. J.*, 2009, **15**, 3509–3525; (e) D. Albrecht, F. Vogt and T. Bach, *Chem. – Eur. J.*, 2010, **16**, 4284–4296; (f) S. C. Coote and T. Bach, *J. Am. Chem. Soc.*, 2013, **135**, 14948–14951.

6 Reviews on enantioselective photochemistry: (a) Y. Inoue, *Chem. Rev.*, 1992, **92**, 741–770; (b) C. Müller and T. Bach, *Aust. J. Chem.*, 2008, **61**, 557–564; (c) C. Yang and Y. Inoue, *Chem. Soc. Rev.*, 2014, **43**, 4123–4143; (d) R. Brimiouille, D. Lenhart, M. M. Maturi and T. Bach, *Angew. Chem., Int. Ed.*, 2015, **54**, 3872–3890.

7 (a) H. Bergmann, B. Grosch, S. Sitterberg and T. Bach, *J. Org. Chem.*, 2004, **69**, 970–973; (b) A. Bakowski, M. Dressel, A. Bauer and T. Bach, *Org. Biomol. Chem.*, 2011, **9**, 3516–3529.

8 (a) R. D. Broene and F. Diederich, *Tetrahedron Lett.*, 1991, **32**, 5227–5230; (b) J. R. Jones, C. L. Liotta, D. M. Collard and D. A. Schiraldi, *Macromolecules*, 1999, **32**, 5786–5792.

9 (a) F. Voss and T. Bach, *Synlett*, 2010, 1493–1496; (b) F. Voss, F. Vogt, E. Herdtweck and T. Bach, *Synthesis*, 2011, 961–971.

10 N. Boens, W. Qin, N. Basarić, J. Hofkens, M. Ameloot, J. Pouget, J.-P. Lefèvre, B. Valeur, E. Gratton, M. vandeVen, N. D. Silva, Y. Engelborghs, K. Willaert, A. Sillen, G. Rumbles, D. Phillips, A. J. W. G. Visser, A. van Hoek, J. R. Lakowicz, H. Malak, I. Gryczynski, A. G. Szabo, D. T. Krajcarski, N. Tamai and A. Miura, *Anal. Chem.*, 2007, **79**, 2137–2149.

11 D. V. O'Connor and D. Phillips, *Time-correlated single photon counting*, Academic Press, London, 1984.

12 J. R. Platt, *J. Chem. Phys.*, 1949, **17**, 484–495.

13 For the determination of K_a , the fluorescence band assigned to the 4'-0 transition (4'-0) was employed. Fluorescence occurs from higher vibrational states (4' or 3') of S_1 to the ground state of S_0 .

14 (a) S. Grimme, J. Antony, S. Ehrlich and H. Krieg, *J. Chem. Phys.*, 2010, **132**, 154104; (b) S. Grimme, S. Ehrlich and I. Goerigk, *J. Comput. Chem.*, 2011, **32**, 1456–1465; (c) J. Tao, J. P. Perdew, V. N. Staroverov and G. E. Scuseria, *Phys. Rev. Lett.*, 2003, **91**, 146401.

15 It remains open whether a rotation occurs within complex **1·6** or whether the equilibrium between **1·6-I** and **1·6-II** is established by a decomplexation-recomplexation equilibrium.

16 I. Baraldi and G. Ponterini, *THEOCHEM*, 1985, **122**, 287–298.

17 (a) O. Christiansen, H. Koch and P. Jørgensen, *Chem. Phys. Lett.*, 1995, **243**, 409–418; (b) C. Hättig and F. Weigend, *J. Chem. Phys.*, 2000, **113**, 5154–5161; (c) C. Hättig and A. Köhn, *J. Chem. Phys.*, 2002, **117**, 6939–6951.

18 (a) I. Warnke and F. Furche, *Wiley Interdiscip. Rev.: Comput. Mol. Sci.*, 2012, **2**, 150–166; (b) C. Diedrich and S. Grimme, *J. Phys. Chem. A*, 2003, **107**, 2524–2539; (c) Y. Nakai, T. Mori and Y. Inoue, *J. Phys. Chem. A*, 2012, **116**, 7372–7385; (d) Y. Nakai, T. Mori and Y. Inoue, *J. Phys. Chem. A*, 2013, **117**, 83–93; (e) Y. Nakai, T. Mori, K. Sato and Y. Inoue, *J. Phys. Chem. A*, 2013, **117**, 5082–5092.

