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Unprecedented 1,3-Dipolar Cycloaddition: From 1,4,5,8-Naphthalene Bisimides to a New Heterocyclic Skeleton

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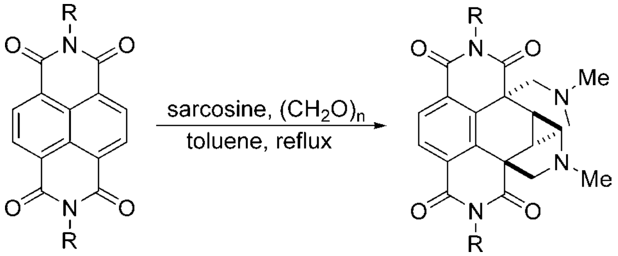
ABSTRACT



1,4,5,8-Naphthalene bisimides react as dipolarophiles with in situ formed azomethine ylides. Double 1,3-dipolar cycloaddition is followed by unique ring rearrangement and leads to the formation of two six-membered rings. The formation of hexacyclic products is rationalized based on DFT calculations.

Naphthalene-1,4,5,8-tetracarboxylic bisimides are often used in applications such as electron donor−acceptor dyes and molecular machines.[1] Even though bisimides are easily prepared by the reaction of bisanhydride and amines, further modifications were usually performed on the peripheral moieties while the core of the molecule remains unchanged. The only known core modification of naphthalene bisimides consists of first halogenation and then transformation via cross-coupling or nucleophilic substitution reactions.[2]

1,3-Dipolar cycloaddition is an extremely popular synthetic method for the construction of heterocycles.[3,4] A diverse range of dipoles and dipolarophiles as well as catalysts (including chiral catalysts) are used to obtain various heterocyclic skeletons. Among these 1,3-dipoles, azomethine ylides are ubiquitously used for the construction of biologically active compounds and electron donor−acceptor dyads.[5] However, only a few examples of the addition of these reactive species to aromatic compounds can be found.[6] Here, we would like to present the serendipitous discovery of a 1,3-cycloaddition reaction of 1,4,5,8-naphthalene bisimides with azomethine ylides leading to hexacyclic products.

In the course of our investigations on the synthetic possibilities in the construction of electron donor−acceptor systems, we performed the reaction of *trans*-A_2B_2-porphyrins, bearing a naphthalene-1,4,5,8-bisimide unit at the *meso*

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(1) (a) Bhosale, S. V.; Jani, C. H.; Langford, S. J. *Chem. Soc. Rev.* **2008**, *37*, 331. (b) Bhosale, S.; Sisson, A. L.; Talukdar, P.; Fürstenberg, A.; Banerji, N.; Vauthey, E.; Bollot, G.; Mareda, J.; Röger, C.; Würthner, F.; Sakai, N.; Matile, S. *Science* **2006**, *313*, 84. (c) Kaik, M.; Gawroński, J. *Org. Lett.* **2006**, *8*, 2921.

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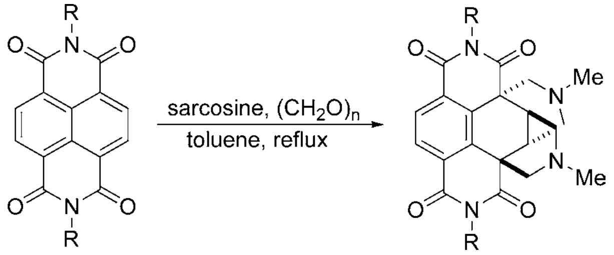
positions, with dipoles generated in situ from sarcosine and paraformaldehyde. Surprisingly, multiple products were formed, but none of them was the expected chlorin. Moreover, the absorption spectra of these products proved that the porphyrin skeleton remained untouched. This suggested that the naphthalene bisimide moiety (rather than porphyrin part) reacted either with formaldehyde or with sarcosine or both. To test this hypothesis, we performed a series of reactions with *N*,*N*′-dioctyl-1,4,5,8-naphthalenetetracarboxylic acid bisimide (**1**) and sarcosine or paraformaldehyde in boiling toluene. In both cases, no reaction took place and the substrate was recovered quantitatively. Consequently, bisimide **1** was treated with a mixture of paraformaldehyde and sarcosine under the same reaction conditions (Scheme 1). One product had formed and was isolated in 24% yield. The NMR and MS analyses did not lead us to any conclusive results about the structure of the unknown compound. It was found that an analogous product **5** is formed from bisimide **2** (prepared from *n*-decylamine) in 45% yield (Scheme 1). X-ray diffraction study[7] revealed that compound **4** was the product which had formed by double 1,3-dipolar cycloaddition followed by unconventional rearrangement (Scheme 1).

Scheme 1



1 R = *n*-octyl
2 R = *n*-decyl
3 R = Me

4 R = *n*-octyl
5 R = *n*-decyl
6 R = Me

Compound **4** crystallizes without solvent in the $P\bar{1}$ space group (Figure 1a), and the asymmetric unit contains a single molecule. The naphthalene-1,4,5,8-tetracarboxylic bisimide fragment, excluding the place of addition, is almost planar with mean deviation from planarity of ca. 0.1 Å. The six-membered saturated rings adopt a chair conformation, where the methyl groups are equatorial and hence situated perpendicularly in respect to the conjugated fragment. Both octyl side chains are well-ordered, which may be attributed to the specific crystal packing. These fragments are situated in close proximity to each other in the neighboring molecules related by an inversion center. In effect, the layers built of aliphatic chains are formed (see Figure 1b). The molecules are weakly interacting in the crystal lattice; they are mostly stabilized by weak C−H···O contacts (C···O distances = 3.346−3.462 Å) and other types of van der Waals interactions. The DFT optimization at the B3LYP/6-311G** level for an isolated molecule (with octyl groups replaced by methyl ones) is very consistent with the experiment: the mean difference between relevant bond lengths is at the level of 0.005 Å.[8]

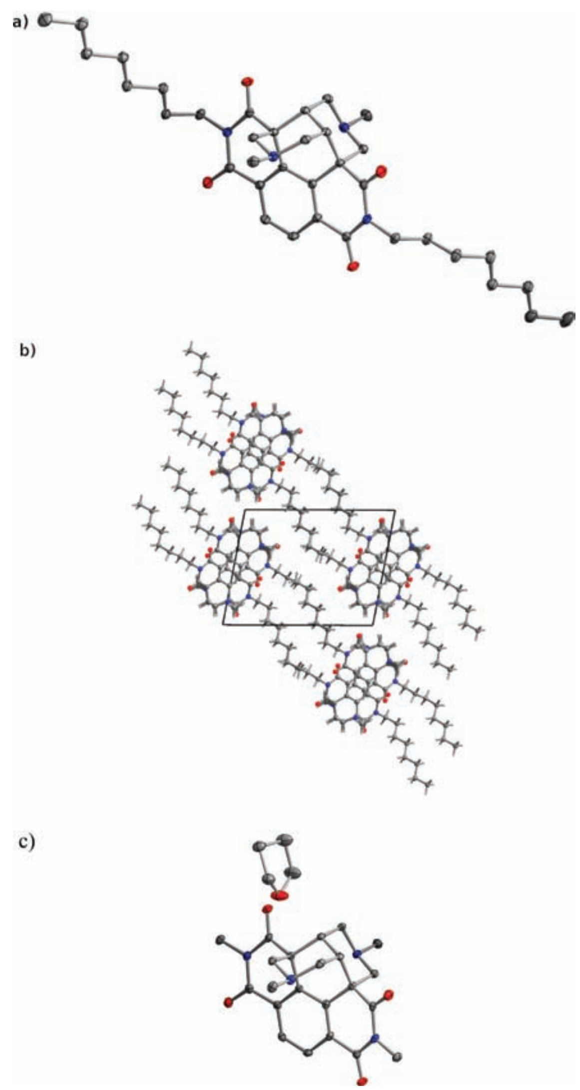


Figure 1. (a) Thermal ellipsoid plot of bisimide **4**. The ellipsoids drawn at 50% probability level, H atoms omitted for clarity. (b) Crystal packing along [100] direction. (c) Thermal ellipsoid plot of bisimide **6** (with THF). The ellipsoids drawn at 50% probability level, H atoms omitted for clarity.

Supposedly, double 1,3-dipolar cycloaddition product **4** with two five-membered rings underwent rearrangement, which resulted in the formation of two six-membered rings. Reactivity of naphthalene-1,4,5,8-tetracarboxylic acid bisimides as dipolarophiles has never been mentioned in the literature. The only related results were reported by Corsaro et al., describing that anthracene and perylene undergo 1,3-dipolar cycloaddition with benzonitrile oxides.[9] Skeleton

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(2) (a) Gao, X.; Qiu, W.; Yang, X.; Liu, Y.; Wang, Y.; Zhang, H.; Qi, T.; Liu, Y.; Lu, K.; Du, C.; Shuai, Z.; Yu, G.; Zhu, D. *Org. Lett.* **2007**, *9*, 3917. (b) Röger, C.; Würthner, F. *J. Org. Chem.* **2007**, *72*, 8070.

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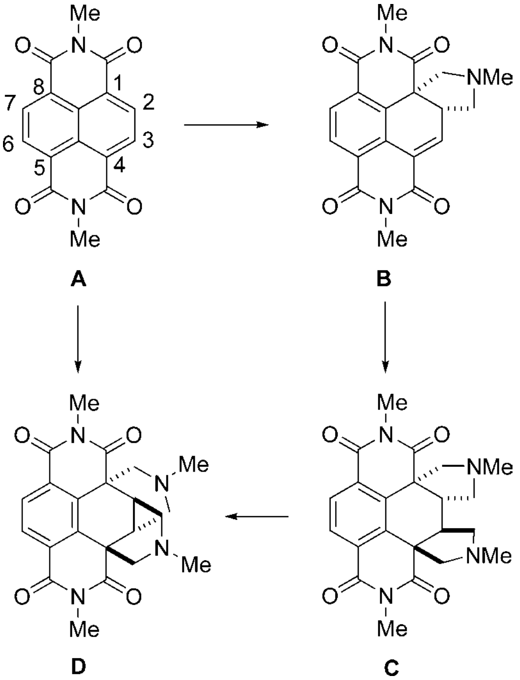
rearrangement of the five-membered product formed in 1,3-dipolar cycloaddition into a six-membered one is yet unknown to the best of our knowledge. Optimization reactions of bisimides **1** and **2** with sarcosine and paraformaldehyde were conducted by increasing the reaction time and changing the ratio of substrates. All attempts failed to increase the yield of bisimides **4** and **5**.

According to the symmetry of dipole HOMO and dipolarophile LUMO (see the Supporting Information for details), the only possible pathway of the reaction must follow intermediates **B** and **C** (Scheme 2). The final concerted rearrangement of two five-membered rings in intermediate **C** seems to lead to strain cancellation and energy minimization. There are three ambiguities concerning this unusual series of reactions, which should be explained and/or quantified: (i) why the reaction follows double, not single, addition; (ii) what is the preferred place of the addition; and (iii) why rearrangements take place. To tackle these problems, DFT calculations at the B3LYP/6-311G** level of theory were performed.[10] This level is known to provide quite accurate energies and reliable geometries for many organic compounds.[11]

Scheme 2



Taking into account the position of the attached dipole, its possible conformational flexibility, and the position of the methyl groups at nitrogens, we have started with 13 molecular geometries with 0, 1, or 2 saturated rings attached, where the octyl groups were replaced by methyl ones for simplicity (see Supporting Information for more details). As a result, lowest energy isomers of bisadducts, the rearranged bisadduct **D**, monoadduct **B**, and the starting naphthalene-1,4,5,8-tetracarboxylic bisimide **A** have been obtained. All structures corresponded to real minima at the potential energy surface with no imaginary frequencies, and the resulting energies were corrected for ZPE correction. At the same level of theory, we have also calculated the transition state of transformation from 1,2,3,4-bisadduct **C** to 1,3,2,4-bisadduct **D**. A stationary has been found and was characterized by one imaginary frequency.

The first two questions may be solved within a homodesmotic approach,[12] by comparison of the energy of 1,2,3,4-bisadduct **C** with 1,2-monoadduct **B** and the parent starting system **A** (see Scheme 3). This kind of theoretical reaction has been proven to be very successful in solving many problems of physical organic chemistry dealing, for example, with substituent effect,[13] aromaticity, or strain energy.[14] Here the estimated energetic balance indicates that the 1,2,3,4-

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(4) (a) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, B. K. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596; *Angew. Chem.* **2002**, *114*, 2708. (b) Kano, T.; Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2005**, *127*, 11926. (c) Kim, S.; Lee, Y. M.; Lee, J.; Lee, T.; Fu, Y.; Song, Y.; Cho, J.; Kim, D. *J. Org. Chem.* **2007**, *72*, 4886–4891. (d) Mmutlane, E. M.; Harris, J. M.; Padwa, A. *J. Org. Chem.* **2005**, *70*, 8055–8063. (e) Alemparte, C.; Blay, G.; Jørgensen, K. A. *Org. Lett.* **2005**, *7*, 4569–4572. (f) St. Cyr, D. J.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2007**, *129*, 12366–12367. (g) Aggarwal, V. K.; de Vicente, J.; Bonnert, R. V. *J. Org. Chem.* **2003**, *68*, 5381–5383. (h) López-Pérez, A.; Adrio, J.; Carretero, J. C. *J. Am. Chem. Soc.* **2008**, *130*, 10084–10085. (i) Ess, D. H.; Houk, K. N. *J. Am. Chem. Soc.* **2007**, *129*, 10646–10647. (j) Kim, Y.; Kim, J.; Park, S. B. *Org. Lett.* **2009**, *11*, 17–20.

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(7) Crystal data for **4**: $C_{36}H_{52}N_4O_4$; $M_r = 604.82$, triclinic, $a = 8.5884(1)$ Å, $b = 12.6747(2)$ Å, $c = 15.8365(2)$ Å, $\alpha = 78.834(1)°$, $\beta = 86.796(1)°$, $\gamma = 77.199(1)°$, $V = 1649.07(4)$ Å^3, $T = 100(2)$ K, space group $P\bar{1}$ (no. 2), $Z = 2$, $\mu = 0.079$ mm^{-1}, $d = 1.218$ g cm^{-3}, $F(000) = 656$, 30 414 reflections collected, 7664 unique ($R_{\mathrm{int}} = 0.0214$) which were used in all calculations, 2θ range 6.2−56.58°, GOF = 0.908. The final R_1 and wR_2 (F_2) were 0.0551 and 0.0877 (all data), 0.0344 and 0.0840 ($I > 2\sigma(I)$). Largest diff. peak and hole: 0.322 and −0.194 eÅ^{-3}. Crystallographic data have been deposited at the Cambridge Crystallographic Data Centre with the deposition number CCDC 763868. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(8) Agreement between the experimental structure of **6** and its optimized structure is also at the same level.

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(10) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian*; Gaussian Inc.: Wallingford, CT, 2004.

(11) De Proft, F.; Geerlings, P. *Chem. Rev.* **2001**, *101*, 1451.

(12) (a) George, P.; Trachtman, M.; Bock, C. W.; Brett, A. M. *Theor. Chem. Acc.* **1975**, *38*, 121. (b) George, P.; Trachtman, M.; Bock, C. W.; Brett, A. M. *Tetrahedron* **1976**, *32*, 317. (c) George, P.; Trachtman, M.; Bock, C. W.; Brett, A. M. *J. Chem. Soc., Perkin Trans. 2* **1976**, 1222. (d) Pross, A.; Radom, L.; Taft, R. W. *J. Org. Chem.* **1980**, *45*, 818.

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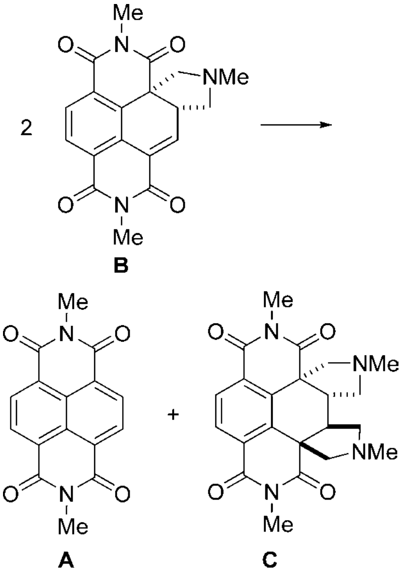
Scheme 3



bisadduct **C** is more stable by 14.0 kcal/mol than the 1,2-monoadduct **B**, so indeed, this compound is thermodynamically preferred. A similar homodesmotic reaction taking into account the other places of addition (e.g., positions 1, 2, 5, 6 or 1, 2, 7, 8) shows the reverse: the 1,2-monoadduct is more stable by 9.8−16.0 kcal/mol (see Supporting Information for details). This can be easily understood. An addition of the dipole to the bisimide enforces aromatic (benzene-like) fragment formation in the other part of the molecule. This fragment is extra stabilized by cyclic λ-electron π-delocalization which prevents the addition reaction.[15]

The third problem concerning the rearrangement can be solved by simple comparison of the total energies of the 1,2,3,4-bisadduct **C** and the 1,3,2,4-bisadduct **D**. As expected, the latter system is more stable by 12.4 kcal/mol. This indicates its thermodynamic preference and obviously is in line with the experimental observations. It is fair to note that the transformation may not be as efficient as one may expect because the estimated barrier of the inversion is very high (ca. 97.7 kcal/mol). Initially, we thought that the entropy factor may be very important for the rearrangement (longer side chains may make the reaction more efficient). To test this hypothesis, bisimide **3** bearing methyl substituents on nitrogen was subjected to the reaction conditions (Scheme 1). Only rearranged cycloadduct **6** was isolated from the reaction mixture (in 78% yield), which suggests that entropy does not play a crucial role. The structure of **6** has been proved by X-ray measurement (Figure 1c).[16] It cocrystallizes with one molecule of THF, and the geometry of the hexacyclic core is similar to that of **4**. Again, the saturated rings adopt a chair conformation, where the methyl groups are equatorial (see Supporting Information for details).

In summary, we have revealed the unprecedented reactivity of naphthalene bisimides as dipolarophiles in 1,3-dipolar cycloaddition with in situ formed azomethine ylides. This is the first example of such a reaction for naphthalene derivatives. The rigid hexacyclic structure formed is unique and can serve as a platform for further transformations. Although many points remained unsolved, such as the reactivity of simpler systems having a similar ring topology and/or other aromatics, and the role and importance of the side chains, etc., our case sheds new light on the 1,3-dipolar cycloaddition mechanism, which has an immense practical impact.

Acknowledgment. The authors acknowledge Polish Ministry of Science and Higher Education (Contract T09A 50612) and thank Keith O'Proinsias for amending the manuscript. The X-ray structures of **4** and **6** were determined in the Crystallographic Unit of the Physical Chemistry Laboratory at the Chemistry Department of the University of Warsaw, and at the Faculty of Chemistry, Warsaw University of Technology, respectively. M.K.C. acknowledges Dr. Izabela Madura for her kind assitance. The ICM (University of Warsaw) is acknowledged for computational facilities.

Supporting Information Available: Experimental details, ^{1}H NMR and ^{13}C NMR spectra for compounds **2**−**6**, X-ray details as well as tables of calculated energy levels. This material is available free of charge via the Internet at http://pubs.acs.org.

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[15] Cyrański, M. K. *Chem. Rev.* **2005**, *105*, 3773.

[16] Crystal data for **6**: $C_{22}H_{24}N_4O_4$, C_4H_8O; M_r = 480.56, triclinic, a = 8.5857(4) Å, b = 9.6072(5) Å, c = 15.1965(11) Å, α = 85.168(5)°, β = 76.462(5)°, γ = 70.470(5)°, V = 1148.52(11) Å^3, T = 100(2) K, space group $P\bar{1}$ (no. 2), Z = 2, μ = 0.097 mm^{-1}, d = 1.390 g cm^{-3}, $F(000)$ = 512, 10 781 reflections collected, 4736 unique (R_{int} = 0.0346) which were used in all calculations, 2θ range 6.4−53.0°, GOF = 0.989. The final R_1 and wR_2 (F_2) were 0.0718 and 0.1188 (all data), 0.0429 and 0.1078 ($I > 2\sigma(I)$). Largest diff. peak and hole: 0.331 and −0.286 eÅ^{-3}. Crystallographic data have been deposited at the Cambridge Crystallographic Data Centre with the deposition number CCDC 772671. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.