[4] U. Kragl, C. Dreisbach, *Angew. Chem.* **1996**, *108*, 684–685; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 642–664.
[5] a) J. B. Flanagan, S. Margel, A. J. Bard, F. C. Anson, *J. Am. Chem. Soc.* **1978**, *100*, 4248; b) F. G. Bordwell, G. D. Cooper, H. Mortina, *J. Am. Chem. Soc.* **1957**, *79*, 376; c) T. W. Smith, J. E. Kunder, D. Wychick, *J. Polym. Sci.* **1976**, *14*, 2433.
[6] a) D. Astruc, *New. J. Chem.* **1992**, *16*, 305; b) D. Astruc, *Top. Curr. Chem.* **1991**, *160*, 47.
[7] a) H. A. U. Hill, D. J. Page, N. J. Walton, *J. Electroanal. Chem.* **1987**, *217*, 141; b) Y. Degani, A. Heller, *J. Phys. Chem.* **1987**, *91*, 1285.
[8] R. Rulkens, A. J. Lough, I. Manners, *J. Am. Chem. Soc.* **1994**, *116*, 797.
[9] I. Manners, *Adv. Mater.* **1994**, *6*, 62.
[10] J.-L. Fillaut, J. Lineares, D. Astruc, *Angew. Chem.* **1994**, *106*, 2540; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2460.
[11] P. Jutzi, C. Batz, B. Neumann, H.-G. Stammler, *Angew. Chem.* **1996**, *108*, 2272; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2118.
[12] a) V. Chandrasekhar, C. G. Schmid, S. D. Burton, J. M. Holmes, R. O. Day, R. R. Holmes, *Inorg. Chem.* **1987**, *26*, 1050; b) R. R. Holmes, C. G. Schmid, V. Chandrasekhar, R. O. Day, J. M. Holmes, *J. Am. Chem. Soc.* **1987**, *109*, 1408; c) K. C. Kumaraswamy, S. Nagabrahmanandrachari, *Phosphorus sulfur silicon Retat. Elem.* **1992**, *65*, 9.
[13] **3**: ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.00$ (t, $J = 7.2$ Hz, 3H; CH_3), 1.54 (m, 4H; CH_2CH_2), 1.91 (m, 2H; $SnCH_2$), 4.14 (s, 5H; C_5H_5), 4.30 (m, 2H; C_5H_4), 4.82 (m, 2H; C_5H_4); ^{119}Sn NMR (150 MHz, $CDCl_3$): $\delta = -486.6$ (s).
[14] Crystallographic data for **3** ($C_{90}H_{108}Fe_6O_{18}Sn_6 \cdot 2.57\,CHCl_3$): crystal dimensions $0.51 \times 0.48 \times 0.40$ mm, $M_r = 2831.96$, triclinic, space group $P\bar{1}$; $a = 15.786(8)$, $b = 16.178(8)$, $c = 24.508(12)$ Å, $\alpha = 91.27(2)$, $\beta = 107.328(18)$, $\gamma = 117.499(14)^\circ$; $Z = 2$, $\rho_{calcd} = 1.807$ Mg m^{-3}, $F(000) = 2794$; absorption coefficient 2.480 mm^{-1}. Intensity data were collected using a Bruker SMART ccd area detector[19] mounted on a Bruker P4 goniometer using graphite-monochromated $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å). The sample was cooled to 138(2) K. The intensity data, which nominally covered 1.5 hemispheres of reciprocal space, were measured as a series of ϕ oscillation frames, each 0.4° for 30 s per frame. The detector was operated in the 512×512 mode and was positioned 5.00 cm from the sample. Coverage of unique data was 97.9% complete to 25.00° in θ. Cell parameters were determined from a nonlinear least-squares fit of 8192 peaks in the range $3.0 < \theta < 25.0^\circ$. The first 50 frames were repeated at the end of data collection and yielded 698 peaks showing a variation of −0.04% during the data collection. A total of 69782 data were measured in the range $1.50 < \theta < 28.34^\circ$. The data were corrected for absorption by the empirical method[20] giving minimum and maximum transmission factors of 0.296 and 0.353. The data were merged to form a set of 24235 independent data with $R(\mathrm{int}) = 0.0483$. The triclinic space group $P\bar{1}$ was determined by statistical tests and verified by subsequent refinement. The structure was solved by direct methods and refined by full-matrix least-squares methods on F^2.[21] The hydrogen atom positions were initially determined by geometry and refined by a riding model. Non-hydrogen atoms were refined with anisotropic displacement parameters. A total of 1414 parameters were refined against 776 restraints and 24235 data to give $wR(F^2) = 0.1107$ and $S = 1.080$ for $w = 1/[\sigma^2(F^2) + (0.0364P)^2 + 25.7453P]$, where $P = [F_o^2 + 2F_c^2]/3$. The final $R(F)$ was 0.0431 for the 18440 observed data ($F > 4\sigma(F)$). The largest shift was 0.046 in the final refinement cycle. The final difference map had maxima and minima of 2.122 and −1.415 e Å^{-3}. Three of the *n*-butyl groups are disordered and each is modeled in two orientations. Three solvent sites are found in the regions of the disordered butyl groups, which are also disordered. A fourth disordered solvent site is located away from the main species and is modeled in three orientations. Restraints were applied to the positional and displacement parameters of the disordered atoms. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-137558. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
[15] B. Grossmann, J. Heinze, E. Herdtweck, F. H. Kohler, H. Noth, H. Schwenk, M. Spiegler, W. Wachter, B. Weber, *Angew. Chem.* **1997**, *109*, 384; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 387.
[16] Cyclic voltammetric and differential pulse voltammetric studies were performed on a PAR model 273A polarographic analyzer utilizing the three-electrode configuration of a Pt (Beckman) working electrode, a Pt mesh counterelectrode, and a commercially available saturated calomel electrode as the reference electrode interfaced with the computer. Half-wave potentials were measured as the average of the cathodic and the anodic peak potentials. The voltammograms were recorded in dichloromethane containing 0.1M tetrabutylammonium hexafluorophosphate as the supporting electrolyte, and the potential was scanned from −1.5 to +1.5 V at scan rates from 25 to 200 mV s^{-1}.
[17] N. Prokopuk, D. F. Shriver, *Inorg. Chem.* **1997**, *36*, 5609.
[18] J.-L. Fillaut, D. Astruc, *J. Chem. Soc. Chem. Commun.* **1993**, 1320.
[19] a) Data Collection: SMART Software Reference Manual Bruker-AXS, 6300 Enterprise Dr., Madison, WI 53719-1173, USA, **1994**; b) Data Reduction: SAINT Software Reference Manual Bruker-AXS, 6300 Enterprise Dr., Madison, WI 53719-1173, USA, **1995**.
[20] G. M. Sheldrick, SADABS, Universität Göttingen, Germany, **1996**.
[21] a) G. M. Sheldrick, SHELXTL, Version 5 Reference Manual, Bruker-AXS, 6300 Enterprise Dr., Madison, WI 53719-1173, USA, **1994**; b) *International Tables for Crystallography, Vol. C*, Tables 6.1.1.4, 4.2.6.8, and 4.2.4.2, Kluwer, Boston, **1995**.

Molecular Signal Transduction through Conformational Transmission of a Perhydroanthracene Transducer**

Rolf Krauss, Hans-Georg Weinig, Matthias Seydack, Jürgen Bendig, and Ulrich Koert*

Signal transduction plays an important role in biological systems.[1] While many processes in biological signal transduction[2, 3] use the diffusion of a "second messenger" to the effector site, a molecular transducer linking the receptor and the effector site offers the advantages of a predictable signal distance and signal direction.[4] Herein we show how conformational transmission[5, 6] can be used to design a synthetic transducer.[7] Novel biconformational perhydroanthracene derivatives[8] were synthesized and successfully used as signal transducers in which conformational transmission occurs via a triple ring flip.[9]

Molecular signal transduction via conformational transmission leads, upon a signal stimulus, to a conformational change at the receptor site (Figure 1a). This motion is transmitted by the transducer to the effector site and a second conformational change results in a measurable effect. A good transducer should show a two-state conformational behavior: Binding of the molecular signal should lead to a switching from one conformational state to the other.[10–13] The

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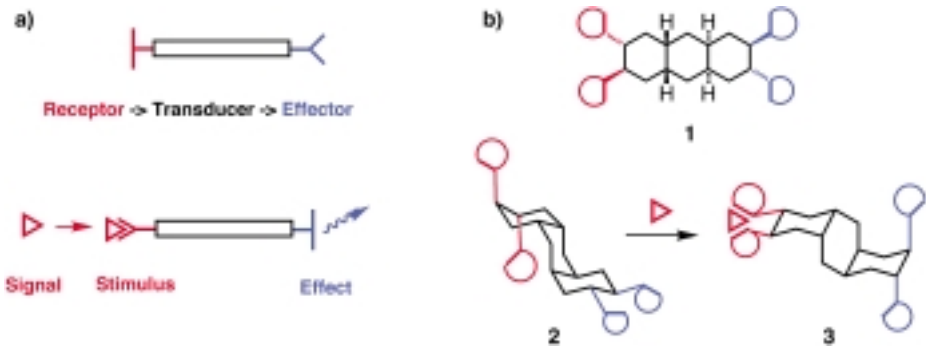

Figure 1. Molecular signal transduction via conformational transmission. a) The signal causes a conformational change at the receptor site, which is carried to the effector site. b) General structure of a tetrasubstituted perhydroanthracene transducer **1** with two receptor sites (red) and two effector sites (blue). The all-chair conformer **2** is converted, upon binding of the signal compound via a triple ring flip, to the all-chair conformer **3**. The equatorial to axial change of the effector substitutents leads to a measurable response.

two all-chair conformers of biconformational[14, 15] *cis-anti-cis*-perhydroanthracene interconvert by a triple ring flip.[8] A tetra-substituted[9] *cis-anti-cis*-perhydroanthracene of type **1** with two receptor substituents (red) and two effector substituents (blue) was chosen as a transducer (Figure 1 b). In conformer **2** the receptor substituents are positioned axially and the effector substituents equatorially. Binding of the signal compound in a chelation mode enforces the conformational switching **2** → **3**. In conformer **3** the receptor substituents have exchanged to equatorial positions and the effector substituents are now at axial positions. Recently, we have shown by X-ray crystal structural analysis that a covalently induced triple ring flip **2** → **3** is possible.[9]

In compound **4**, two 2,2′-bipyridine groups,[16] fixed by an ether linkage to the perhydroanthracene, were chosen as receptor substituents (Figure 2). Pyrene groups were selected as effectors as two pyrene substituents in the equatorial position form an excimer.[17] This excimer exhibits a fluorescence signal at 480 nm. In contrast, two pyrenes positioned axially are sufficiently remote to give only a monomer fluorescence signal at 380 nm.

Different compounds with equatorially and axially located pyrene effectors were synthesized and analyzed spectroscopically. The choice of the linker between the perhydroanthracene transducer and the pyrene effector was found to be crucial. An *E* olefin spacer and an ester group is suited to suppress, to a large extent, excimer formation in the bisaxial conformer. The synthesis of **4** and the reference compounds were based on earlier work[9] (synthetic details and spectroscopic characterization of **4** are given in the Supplementary Information).

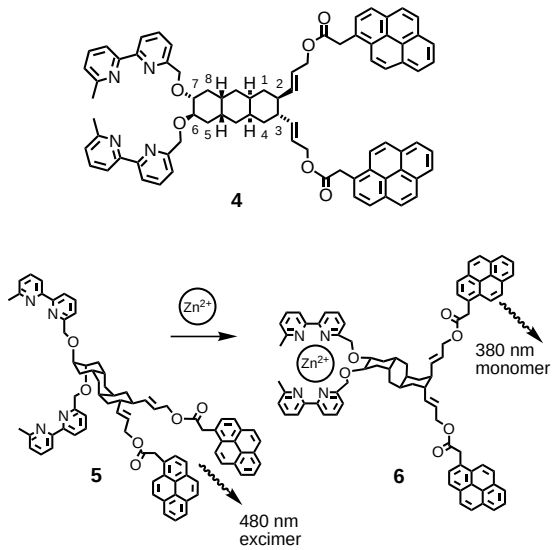

Figure 2. Structure of the perhydroanthracene transducer **4** featuring a bipyridine receptor and a pyrene effector. In solution, compound **4** has the conformation **5** (axial bipyridine substituents, equatorial pyrene sidechains). Upon complexation of a zinc(II) ion, a triple ring flip of the transducer occurs and compound **4** has the conformation **6**. The former equatorial pyrene groups (excimer fluorescence at 480 nm) have switched to axial positions (monomer fluorescence around 380 nm).

NMR spectroscopy of uncomplexed **4** revealed conformer **5** as the only detectable species. The only proton signal of the perhydroanthracene skeleton of **5** with three large coupling constants of $J = 12$ Hz is now $H(1)_\beta$. The two equatorial protons of **5** H(6) and H(7) show three small ^3J coupling constants of 3-4 Hz. The emission fluorescence spectrum of uncomplexed **4** displayed the expected weak pyrene monomer band at around 380 nm and the strong excimer band at 480 nm (Figure 3). Zinc(II) ions and bis-2,2′-bipyridyl ether ligands

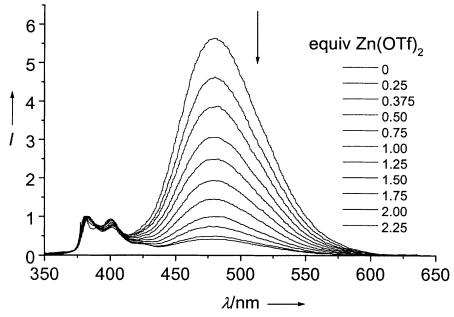

Figure 3. Photoresponse of **4** to the signal (presence of zinc(II)). Fluorescence spectrum[20] of **4** in acetonitrile/chloroform (1/1) as a function of added zinc(II) triflate ($\lambda_{ex} = 343$ nm, $c = 5.6 \cdot 10^{-6}$ mol L^{-1}, $T = 298$ K). Fluorescence spectra were normalized to the monomer peak ($\lambda_{em} =$ 380 nm).

form a chelating complex with the zinc(II) ion coordinated to two bidentate bipyridyl groups and two monodentate ether oxygen atoms.[16] An NMR analysis of the zinc(II) complex of **4** indicated conformational switching[18] from **5** to **6**: The only proton signal of the perhydroanthracene skeleton of **6** with three large coupling constants of $J = 12$ Hz is H_α-C(8) and the two axial protons of **6** H-C(6) and H-C(7) show two large and one small ^3J coupling constants. Addition of zinc(II) ions to compound **4** resulted in a distinct decrease of the excimer band at 480 nm relative to the pyrene monomer fluorescence band at 380 nm (Figure 3).

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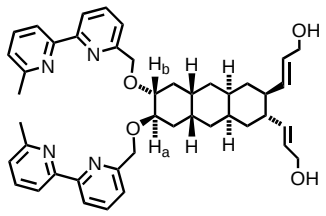
The zinc signal causes a conformational axial to equatorial change at the receptor site, which is transduced via a triple ring flip of the perhydroanthracene moiety to the pyrene effector site, where the induced equatorial to axial flip yields the observed fluorescence photosignal. A UV/Vis titration[19] was used to determine the receptor binding energy necessary to induce the triple ring flip. To avoid spectral overlap due to the pyrene chromophore, compound **7** was studied as a model



7

system (Figure 4a). From a UV/Vis titration of **7** with zinc(II) triflate (Figure 4b) a binding energy of $\Delta G = 7.1$ kcal mol^{-1} in acetonitrile/choroform for the complex $[Zn^{II}\text{-}\mathbf{7}]^{2+}(OTf)_2$ was derived.[19] The triple ring flip of **7** upon addition of zinc(II) was demonstrated by a ^{1}H NMR titration of **7** with zinc(II) triflate (Figure 4c).

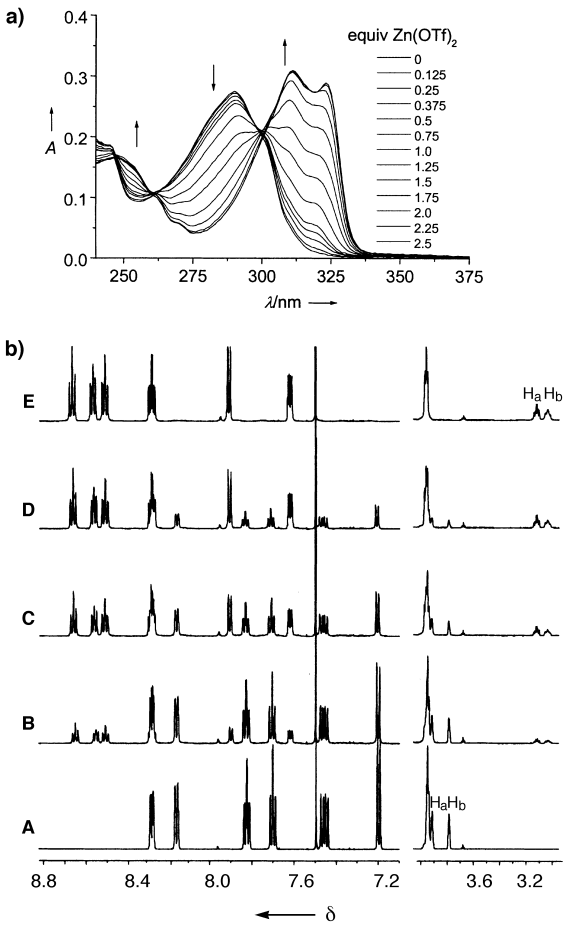


Figure 4. Analysis of the complexation-induced triple ring flip. a) UV/Vis titration of **7** with zinc(II) triflate (acetonitrile/chloroform (1/1), $c = 8.1 \times 10^{-6}$ mol L^{-}, $T = 298$ K). c) ^{1}H NMR titration of **7** with zinc(II) triflate (acetonitrile/chloroform (1/1), $c = 2.9 \times 10^{-2}$ mol L^{-1}). Zinc(II) triflate quantity: A = 0, B = 0.3, C = 0.6, D = 0.9, E = 1.1 equiv.

It is important for functional signal transduction to be reversible: The process needs both an on and off switch. Addition of chelating agents (2,2′-bipyridine or ethylenediaminetetraacetic acid) to the solution of the zinc complex **6** resulted in a distinct increase of the pyrene excimer emission relative to the monomer fluorescence. This is the expected photoresponse for the off switch (**6** → **5**).

In the above example, molecular signal transduction by conformational transmission was demonstrated with a particular receptor–effector pair. One can imagine a variety of stimuli at the receptor site such as photoisomerization or a redox process. An interesting topic of investigation will be the induced dissociation of an ion or ligand at the effector side.

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[1] G. Krauss, *Biochemie der Regulation und Signaltransduktion*, Wiley-VCH, Weinheim, **1997**.
[2] L. B. Ray, *Science* **1999**, *284*, 755–756.
[3] K. Hinterding, D. Alonso-Díaz, H. Waldmann, *Angew. Chem.* **1998**, *110*, 716–780; *Angew. Chem. Int. Ed.* **1998**, *37*, 688–749.
[4] J.-M. Lehn, *Supramolecular Chemistry*, VCH, Weinheim, **1995**.
[5] D. H. R. Barton, *Science* **1970**, *169*, 539–544.
[6] H. Yuasa, H. Hashimoto, *J. Am. Chem. Soc.* **1999**, *121*, 5089–5090.
[7] R. W. Hoffmann, *Angew. Chem.* **1992**, *104*, 1147–1157; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1124–1134.
[8] P. Vanhee, B. van de Graaf, D. Tavernier, J. M. A. Baas, *J. Org. Chem.* **1983**, *48*, 648–652.
[9] J. Berninger, R. Krauss, H.-G. Weinig, U. Koert, B. Ziemer, K. Harms, *Eur. J. Org. Chem.* **1999**, 875–884.
[10] R. A. Bissel, E. Córdova, A. E. Kaifer, J. F. Stoddart, *Nature* **1994**, *369*, 133–137.
[11] L. Gobbi, P. Seiler, F. Diederich, *Angew. Chem.* **1999**, *111*, 737–740; *Angew. Chem. Int. Ed.* **1999**, *38*, 674–678.
[12] P. R. Ashton, V. Balzani, J. Becher, A. Credi, M. C. T. Fyfe, G. Mattersteig, S. Menzer, M. B. Nielsen, F. M. Raymo, J. F. Stoddart, M. Venturi, D. J. Williams, *J. Am. Chem. Soc.* **1999**, *121*, 3951–3957.
[13] J. N. H. Reek, H. Engelkamp, A. E. Rowan, J. A. A. W. Elemans, R. J. M. Nolte, *Chem. Eur. J.* **1998**, *4*, 716–722.
[14] R. W. Hoffmann, I. Münster, *Liebigs Ann.* **1997**, 1143–1150.
[15] A. G. De Oliveira Santos, W. Klute, J. Torode, V. P. W. Böhm, E. Cabrita, J. Runsink, R. W. Hoffmann, *New. J. Chem.* **1998**, 993–997.
[16] A. Bilyk, M. M. Harding, P. Turner, T. W. Hambley, *J. Chem. Soc. Dalton Trans.* **1994**, 2783–2790.
[17] a) I. Aoki, T. Harada, T. Sakaki, Y. Kawahara, S. Shinkai, *J. Chem. Soc. Chem. Commun.* **1992**, 1341–1345; b) A. P. de Silva, H. Q. N. Gunaratne, T. Gunnlaugsson, A. J. M. Huxley, C. P. McCoy, J. T. Rademacher, T. E. Rice, *Chem. Rev.* **1997**, *97*, 1515–1566.
[18] M. Raban, D. L. Burch, E. R. Hortelano, D. Durocher, D. Kost, *J. Org. Chem.* **1994**, *59*, 1283–1287.
[19] R. Foster, *Organic Charge–Transfer Complexes*, Academic Press, London, **1969**, p. 128.
[20] H. Braatz, S. Hecht, H. Seifert, S. Helm, J. Bendig, W. Rettig, *J. Photochem. Photobiol. A* **1999**, *123*, 99–108.

  0570-0833/00/3910-1837 $ 17.50+.50/0