Inclusion Complexes

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Selective Guest Exchange in Encapsulation Complexes Using Light of Different Wavelenghts**

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Reversible control over the state of host–guest encapsulation complexes is a topic of current interest, and at least as many different methods are conceivable as there are unique hosts.[1–5] The task is to trigger the exchange of guests by an "external" signal *after* the initial assembly is generated. The use of light to accomplish this exchange has appeal, because no additional components are introduced into the system and application of the signal is easily done.[6] Accordingly, light has been used as early as 1979 to manipulate the state of host–guest complexes in cyclodextrins.[7,8] Much more recently, we applied this method to control encapsulation in our hydrogen-bonded capsule **1·1** and in the extended capsule **1·2$_4$·1** (Figure 1 a) by using azobenzenes as light-switchable dummy guests.[9] With this refinement, we were able to control the guest that is encapsulated and even the type of assembly that is present in solution. A supramolecular fluorescence switch that is operated by light and heat was constructed as a second-generation system.[10] For an increased information, a corresponding escalation in "input" structures is necessary, and a system that responds differently to different wavelengths of light is a likely first step. Systems already exist that show such multi-light input responses, but their photoresponsive entities are usually covalently connected.[11–14] A supramolecular system that uses different wavelengths of light to selectively affect guest exchange has not been available; herein, we report a wavelength-dependent and sequential light-triggered guest exchange from two different assemblies.

For this sequence we developed a second "dummy" guest, which can be extruded from the capsular hosts by photoisomerization at a wavelength complementary to that of azobenzene (365 nm). Hemithioindigo (HTI) appeared promising, because it is readily isomerized at longer wavelengths (typically 410 to 430 nm) with high efficiency while showing very little photofatigue.[15–18] The back-isomerization can either be achieved by irradiation at wavelengths higher than 480 nm or by simple heating. Because of these advantages, HTI is increasingly applied as photoswitch: to embed in membranes,[19,20] to manipulate the folding of peptides,[21] to change the potency of an inhibitor by irradiation,[22] or to control ionic currents in gramicidin channels.[23] Applications in supramolecular chemistry are still a novelty.[24]

One additional requirement was a change in shape, from a linear structure (a congruent guest) to a bent structure (an inconvenient shape) upon photoisomerization. The core HTI without any substituents does not show that feature, because both *E* and *Z* isomers have an easily accommodated shape. Appropriate groups on the aromatic rings result in a bent shape of one isomer and a (more-or-less) linear shape for the other. Methyl substitutions at both the 5-position of the heterocycle and at the *para*-position of the stilbene unit (HTI **3**)[25] were found to be effective: the *Z* isomer of **3** is encapsulated exclusively in **1·1** in the presence of the inferior guest *n*-tridecane; on irradiation at 410 nm for 80 min the guests are completely exchanged, with *n*-tridecane encapsulated and the *E* isomer of **3** present in solution. Heating that solution to 160 °C for 6 min restores the starting state. The system can be cycled many times (Figure 1 b and Figure S3 in the Supporting Information). A similar photoregulated guest exchange is possible in the extended assembly **1·2$_4$·1**, when the longer HTI **4,** bearing an *n*-pentyl chain at the *para*-position of the stilbene unit, is employed as the switchable guest together with excess *p*-cymene as the secondary guest (see Figure 1 c and Figure S6 in the Supporting Information). Three social isomers of *p*-cymene are possible in **1·2$_4$·1**, but only two are observed, as previously described[26] (only one social isomer is depicted in Figure 2). The syntheses of HTIs **3** and **4** are given in the Supporting Information and follow established literature procedures[19,20,25,27] starting from commercially available *p*-toluenethiol.

Next, we investigated the photoswitching behavior of a mixture of HTI **3** (a prospective guest for **1·1**) and the long 4-methyl-4′-*n*-hexylazobenzene **5** (a prospective guest for **1·2$_4$·1**) at different wavelengths. At short wavelengths (350 nm) both dyes isomerize, which prevented selective switching. However, at wavelengths of 410 to 430 nm it was possible to isomerize HTI **3** leaving the azobenzene unchanged (data are shown in Figure S7 in the Supporting Information). These experiments augured well for the sequential guest exchange of two different assemblies: the HTI dummy guest was first isomerized using light at a wavelength of $\geq$410 nm to trigger the first exchange; then the azobenzene dummy guest could be expelled from its assembly by irradiation at approximately 365 nm to affect the second guest exchange. The *trans*-4,4′-dimethylazobenzene (*trans*-**6**) is a very good guest for capsule **1·1**, but the longer azobenzene *trans*-**5** is only a mediocre guest for the extended assembly **1·2$_4$·1**. Since the azobenzene-occupied assembly should be

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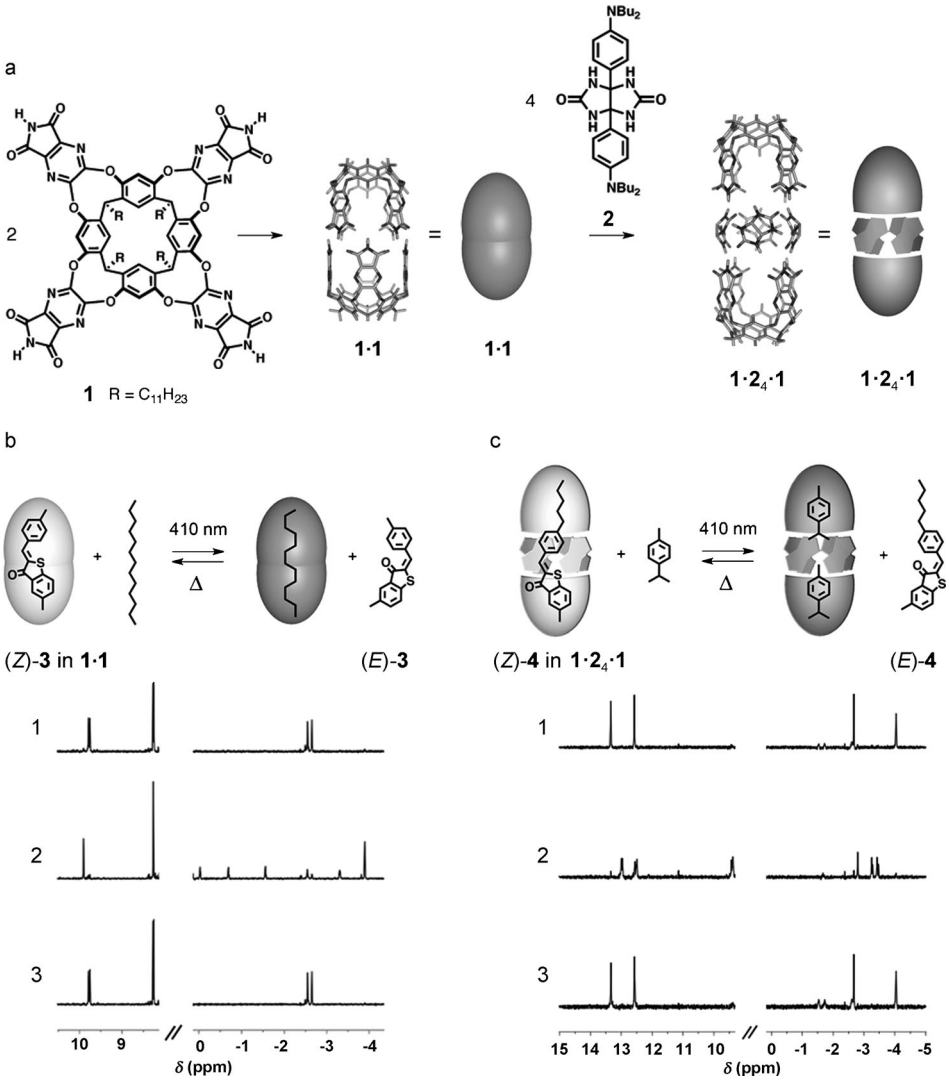

Figure 1. Light-induced guest exchange at 410 nm. a) Capsular assemblies **1·1** and **1·2$_4$·1**. b) Light-induced guest exchange of HTI **3** by *n*-tridecane in **1·1**. c) Light-induced guest exchange of HTI **4** by *p*-cymene in **1·2$_4$·1**. Indicative regions of the ^{1}H NMR spectra ([D$_{12}$]mesitylene, 20 °C) are shown before irradiation (1: (*Z*)-HTI is the only guest) and after irradiation at 410 nm wavelength for 80 min at 20 °C (2: the secondary guest is encapsulated). After heating the sample to 160 °C for six minutes, the initial state was completely restored (3: the (*Z*)-HTI is the only guest).

stable under irradiation conditions for HTI isomerization, we used the most stable azobenzene assembly. Accordingly, the shorter *trans*-**6** was employed as the switchable guest for capsular assembly **1·1** and the longer HTI (*Z*)-**4** as the switchable guest for the extended assembly **1·2$_4$·1**.

When a solution containing cavitand **1** (one equivalent), glycoluril **2** (2.2 equivalents), HTI **4** (0.85 equivalents), azobenzene **6** (0.85 equivalents), 4,4′-dibromobenzil (0.43 equivalents), and *p*-cymene (1.7 equivalents) is heated to 160 °C for six minutes and then cooled, only two assemblies are observed in a 1:1 ratio: an extended capsule **1·2$_4$·1** occupied by the long HTI (*Z*)-**4** and the shorter dimeric capsule **1·1** occupied by *trans*-**6**. Both *p*-cymene and 4,4′-dibromobenzil remain free in solution. HTI **4** is too long to be encapsulated in the dimeric capsule **1·1** and azobenzene **6** is too short to be a good guest for the extended assembly **1·2$_4$·1**. The secondary guests *p*-cymene and 4,4′-dibromobenzil were chosen, because they are inferior guests compared to the respective dyes (*Z*)-**4** and *trans*-**6**, and because they also show no "cross-talk" that is, *p*-cymene is not a guest for the capsule **1·1** and the benzil is not a guest for the extended assembly **1·2$_4$·1**. On heating, an equilibrium is reached in which the capsular assemblies "select" the best fitting occupants for their respective inner spaces.

The sequential guest exchange was started by irradiation at 430 nm with low intensity. After 11 h, the guest exchange in the extended capsule was complete, but no guest exchange occurred in the smaller assembly **1·1** (Figure 2). A new state of the system is established wherein *p*-cymene occupies the extended assembly **1·2$_4$·1** and *trans*-**6** occupies **1·1**. This solution can now either be heated to 160 °C for six minutes to revert to the starting point, or be irradiated at 365 nm with light of high intensity for 20 min to exchange guests in the dimeric capsule **1·1** (Figure 3). In the latter case, a third state of the system is reached wherein *p*-cymene occupies the extended assembly **1·2$_4$·1** and 4,4′-dimethylbenzil occupies **1·1**. After heating that solution to 160 °C for six minutes the system is reset: the original distribution of species is restored, and a new cycle can be started.

Alternatively, it is possible to exchange guests in both assemblies at the same time by irradiation of the solution with intense light at 365 nm for 1.5 h (Figure S10 in the Supporting Information). Again, brief heating restores the starting state. In this way, we achieved a selective, sequential guest exchange.

In a control experiment *trans*-**6** was encapsulated in **1·1** in the presence of 4,4′-dimethylbiphenyl, and this solution was irradiated with 420–550 nm light of the same intensity used for the experiments before. At these wavelengths up to 50 % guest exchange is observed after one hour (see Figure S11 in the Supporting Information)—a result that seemingly contradicts the inert response of this assembly in the full system discussed above. Moreover, no *cis*-azobenzene is observed,

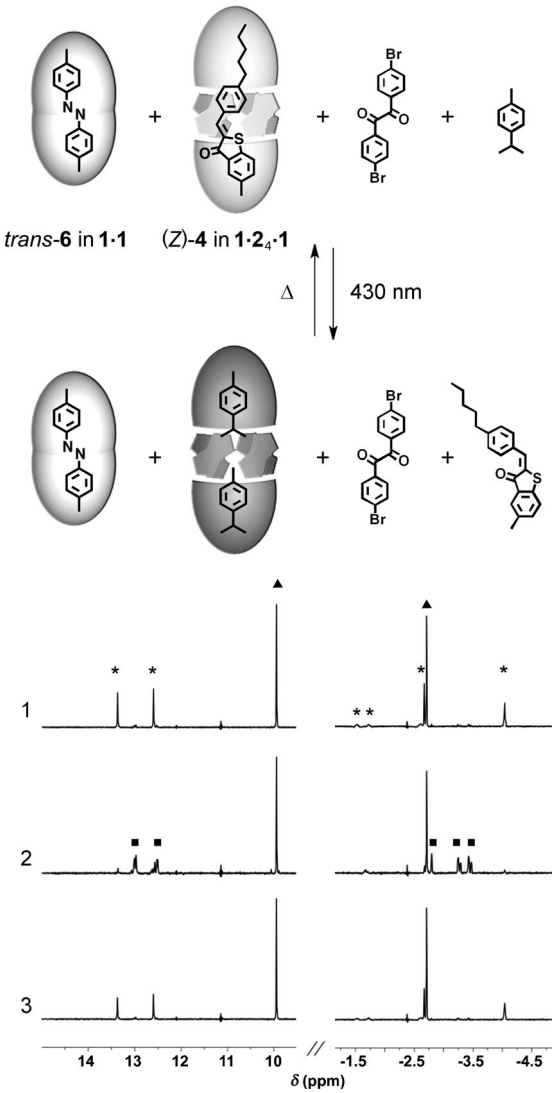

Figure 2. Selective light-induced guest exchange in the extended assembly **1·2$_4$·1** in the presence of unaltered assembly **1·1**. Indicative regions of the ^{1}H NMR spectra ([D$_{12}$]mesitylene, 20 °C) are shown before irradiation (1: (*Z*)-**4** is the guest in **1·2$_4$·1** (*) and *trans*-**6** is the guest in **1·1** (▲)) and after irradiation at 430 nm wavelength for 11 h at 20 °C (2: pairs of *p*-cymene occupy **1·2$_4$·1** (■) and *trans*-**6** remains in **1·1**). After heating the sample to 160 °C for six minutes, the initial state was completely restored (3).

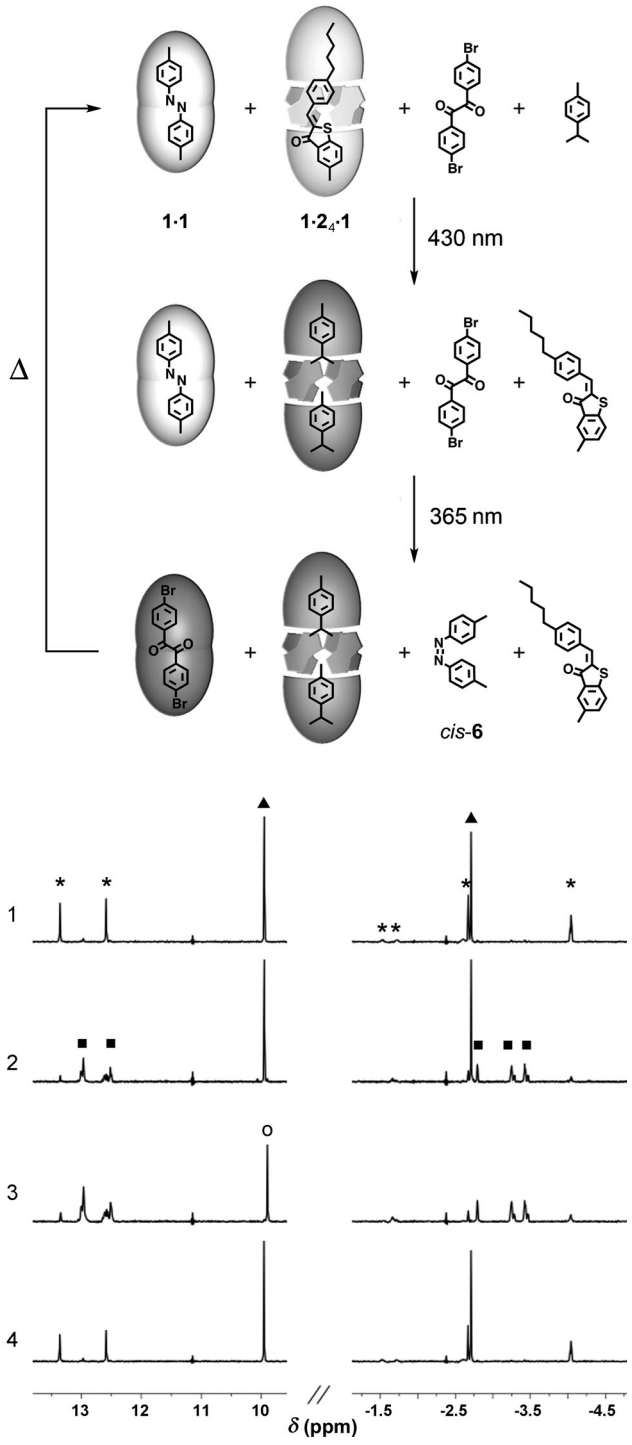

Figure 3. Sequential light-induced guest exchange in the assemblies **1·2$_4$·1** and **1·1**. Three different states of the system can be addressed by light of two different wavelengths and heat. Indicative regions of the ^{1}H NMR spectra ([D$_{12}$]mesitylene, 20 °C) are shown before irradiation (1: (*Z*)-**4** is the guest in **1·2$_4$·1** (*) and *trans*-**6** is the guest in **1·1** (▲)), after the first irradiation at 430 nm wavelength for 11 h at 20 °C (2: pairs of *p*-cymene occupy **1·2$_4$·1** (■) and *trans*-**6** remains in **1·1**), and after the second irradiation at 365 nm wavelength for 20 min at 20 °C (3: pairs of *p*-cymene occupy **1·2$_4$·1** and 4,4′-dibromobenzil occupies **1·1** (○)). After heating the sample to 160 °C for six minutes, the initial state was completely restored (4).

but only *trans*-**6** free in solution. Azobenzenes that are excited at $\geq$410 nm undergo n–π* transition leading to *trans*-to-*cis* isomerization and *cis*-to-*trans* isomerization via the S$_1$-excited state. To relax back to the ground state a geometrical change via the inversion mechanism takes place.[28] As the absorption of *cis*-azobenzenes is stronger compared to the *trans*-isomer at $\geq$410 nm, any generated *cis*-isomer is excited preferably, and overall only *trans*-isomer is obtained at the photostationary state. If the light intensity is increased, complete guest exchange is possible by using 460 nm light with production of only *trans*-**6** outside the capsules in solution. In this experiment 4,4′-dibromobenzil was employed as the second guest (see Figure S12 in the Supporting Information).

In the complete system the situation is somewhat different, because the absorption intensity of the n–π* transition of *trans*-**6** is very low compared to the absorption of HTI (*Z*)-**4** at that wavelength (see Figure S13 in the Supporting Information for the respective UV/Vis absorption spectra). Accordingly, in the complete system the strong absorption of HTI (*Z*)-**4** leaves azobenzene *trans*-**6** unaffected, and no guest exchange involving the latter is seen.

In summary, we have engineered light-triggered guest exchange in two modes using capsule **1**·**1** and the extended assembly **1**·$\mathbf{2}_4$·**1**. The different absorption profiles of HTI and azobenzene dyes were exploited to affect guest exchange either in a sequential or a parallel fashion. This represents a heightened level of control over the encapsulation state in host–guest systems by the simple signals light and heat. We intend to devise more complex light-controlled devices in the future.

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[1] For examples of guest exchange using acid–base chemistry see: a) D. Ajami, J. Rebek, Jr., *J. Am. Chem. Soc.* **2006**, *128*, 15038 – 15039; b) N. Branda, R. M. Grotzfeld, C. Valdés, J. Rebek, Jr., *J. Am. Chem. Soc.* **1995**, *117*, 85 – 88; c) T. Gottschalk, B. Jaun, F. Diederich, *Angew. Chem.* **2007**, *119*, 264 – 268; *Angew. Chem. Int. Ed.* **2007**, *46*, 260 – 264; d) J. Hornung, D. Fankhauser, L. D. Shirtcliff, A. Praetorius, W. B. Schweizer, F. Diederich, *Chem. Eur. J.* **2011**, *17*, 12362 – 12371.

[2] For control of guest exchange using spinning disk processing see: K. Swaminathan Iyer, M. Norret, S. J. Dalgarno, J. L. Atwood, C. L. Raston, *Angew. Chem.* **2008**, *120*, 6462 – 6466; *Angew. Chem. Int. Ed.* **2008**, *47*, 6362 – 6366.

[3] For recent examples of guest exchange using light as trigger see: a) O. B. Berryman, A. C. Sather, A. Lledó, J. Rebek, Jr., *Angew. Chem.* **2011**, *123*, 9572 – 9575; *Angew. Chem. Int. Ed.* **2011**, *50*, 9400 – 9403; b) O. Berryman, A. Sather, J. Rebek, Jr., *Chem. Commun.* **2011**, *47*, 656 – 658; c) G. H. Clever, S. Tashiro, M. Shionoya, *J. Am. Chem. Soc.* **2010**, *132*, 9973 – 9975.

[4] For examples of using light to control ion exchange in ion channels see: a) M. R. Banghart, A. Mourot, D. L. Fortin, J. Z. Yao, R. H. Kramer, D. Trauner, *Angew. Chem.* **2009**, *121*, 9261 – 9265; *Angew. Chem. Int. Ed.* **2009**, *48*, 9097 – 9101; b) M. Banghart, K. Borges, E. Isacoff, D. Trauner, R. H. Kramer, *Nat. Neurosci.* **2004**, *7*, 1381 – 1386; c) A. Koçer, M. Walko, W. Meijberg, B. L. Feringa, *Science* **2005**, *309*, 755 – 758.

[5] For recent examples of light-switchable protein inhibitors see: a) D. Vomasta, C. Högner, N. R. Branda, B. König, *Angew. Chem.* **2008**, *120*, 7756 – 7759; *Angew. Chem. Int. Ed.* **2008**, *47*, 7644 – 7647; b) D. Fujita, M. Murai, T. Nishioka, H. Miyoshi, *Biochemistry* **2006**, *45*, 6581 – 6586.

[6] O. B. Berryman, H. Dube, J. Rebek, Jr., *Isr. J. Chem.* **2011**, *51*, 700 – 709.

[7] A. Ueno, H. Yoshimura, R. Saka, T. Osa, *J. Am. Chem. Soc.* **1979**, *101*, 2779 – 2780.

[8] A. Ueno, K. Takahashi, T. Osa, *J. Chem. Soc. Chem. Commun.* **1980**, 837 – 838.

[9] H. Dube, D. Ajami, J. Rebek, Jr., *Angew. Chem.* **2010**, *122*, 3260 – 3263; *Angew. Chem. Int. Ed.* **2010**, *49*, 3192 – 3195.

[10] H. Dube, M. R. Ams, J. Rebek, Jr., *J. Am. Chem. Soc.* **2010**, *132*, 9984 – 9985.

[11] V. Balzani, A. Credi, M. Venturi, *Chem. Soc. Rev.* **2009**, *38*, 1542 – 1550.

[12] K. Szaciłowski, *Chem. Rev.* **2008**, *108*, 3481 – 3548.

[13] J. Andréasson, U. Pischel, S. D. Straight, T. A. Moore, A. L. Moore, D. Gust, *J. Am. Chem. Soc.* **2011**, *133*, 11641 – 11648.

[14] D. Gust, T. A. Moore, A. L. Moore, *Chem. Commun.* **2006**, 1169 – 1178.

[15] K. Ichimura, T. Seki, T. Tamaki, T. Yamaguchi, *Chem. Lett.* **1990**, 1645 – 1646.

[16] T. Cordes, T. Schadendorf, K. Rück-Braun, W. Zinth, *Chem. Phys. Lett.* **2008**, *455*, 197 – 201.

[17] T. Cordes, T. Schadendorf, B. Priewisch, K. Rück-Braun, W. Zinth, *J. Phys. Chem. A* **2008**, *112*, 581 – 588.

[18] J. Plötner, A. Dreuw, *J. Phys. Chem. A* **2009**, *113*, 11882 – 11887.

[19] K. Eggers, T. M. Fyles, P. J. Montoya-Pelaez, *J. Org. Chem.* **2001**, *66*, 2966 – 2977.

[20] T. Seki, T. Tamaki, T. Yamaguchi, K. Ichimura, *Bull. Chem. Soc. Jpn.* **1992**, *65*, 657 – 663.

[21] T. Cordes, D. Weinrich, S. Kempa, K. Riesselmann, S. Herre, C. Hoppmann, K. Rück-Braun, W. Zinth, *Chem. Phys. Lett.* **2006**, *428*, 167 – 173.

[22] S. Herre, T. Schadendorf, I. Ivanov, C. Herrberger, W. Steinle, K. Rück-Braun, R. Preissner, H. Kuhn, *ChemBioChem* **2006**, *7*, 1089 – 1095.

[23] T. Lougheed, V. Borisenko, T. Hennig, K. Rück-Braun, G. A. Woolley, *Org. Biomol. Chem.* **2004**, *2*, 2798 – 2801.

[24] K. Tanaka, K. Kohayakawa, S. Iwata, T. Irie, *J. Org. Chem.* **2008**, *73*, 3768 – 3774.

[25] G. A. Yugai, M. A. Mostoslavskii, V. D. Paramonov, *Teor. Eksp. Khim.* **1976**, *12*, 700 – 704.

[26] D. Ajami, J. Rebek, Jr., *J. Org. Chem.* **2009**, *74*, 6584 – 6591.

[27] M. T. Konieczny, W. Konieczny, *Heterocycles* **2005**, *65*, 451 – 464.

[28] T. Nägele, R. Hoche, W. Zinth, J. Wachtveitl, *Chem. Phys. Lett.* **1997**, *272*, 489 – 495.

