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Digest Paper

Hemithioindigo—an emerging photoswitch

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ABSTRACT

Hemithioindigo (HTI) is an emerging photoswitch with many advantageous properties compared to the commonly used photoswitches like azobenzenes, spiropyranes, or dithienylethenes. In this DIGEST the syntheses, physical and photophysical properties of HTI photoswitches and mechanistic explanations for the latter are reviewed. Emphasis will be placed on those distinct properties that render HTIs into unique phototools. Additionally, a broad variety of applications ranging from supramolecular to biological chemistry is presented to highlight the great potential of HTIs as upcoming, alternative photoswitches.

Contents

Introduction

Photoswitches undergo reversible changes between two—or sometimes more—molecular states by simple irradiation with light. Because of that property, they have attracted tremendous attention as molecular control unit and have been used in almost every chemistry-related field from material sciences[1] to biology.[2] Many different classes of photoswitches are established to date, making it possible to choose from a variety of photoinduced property changes depending on the specific application. Azobenzenes[3] or stilbenes[4] for instance, allow to induce strong geometrical changes in response to irradiation, whereas photoswitching of spiropyranes[5] or dithienylethenes[6] leads to significant changes of electronic properties.

Compared to the most commonly used azobenzenes, spiropyranes, or dithienylethenes hemithioindigos (HTIs) constitute a rather underexplored class of photoswitches, despite their distinct and very interesting physical and photophysical properties (see Table 1 for a comparison of properties between HTI and common photoswitches). In this DIGEST we will emphasize the most important properties of HTIs and show how they can rationally be altered and exploited in new and exciting applications.

HTIs are unsymmetrical molecules consisting of a thioindigo fragment, which is connected to a stilbene fragment via a central double bond (Fig. 1). This central double bond can be photoisomerized between the *Z* and *E* configurations, with the *Z* configuration being the thermodynamically stable and *E* being the metastable form. The barrier for the thermal *E*/*Z* isomerization of HTIs (typically >27 kcal/mol) is significantly higher than the corresponding barrier for the thermal *cis*/*trans* isomerization of the most commonly used azobenzenes (ca. ⩽25 kcal/mol),[7] making HTIs an intrinsically very bistable switching system. Only the most recent developments have made azobenzene photoswitches available

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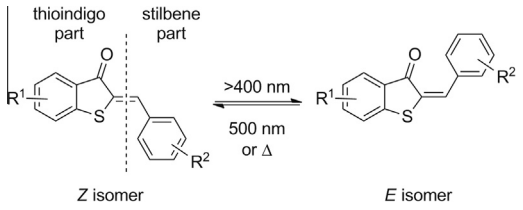


Figure 1. HTI photoswitches consist of a thioindigo and a stilbene part. Photoisomerization from the thermodynamically stable *Z* to the metastable *E* isomer and vice versa is possible using exclusively visible light (>400 nm).

that can be photoisomerized with visible light and maintain high thermal bistability.[8]

The most interesting property of HTIs is their red shifted absorption, allowing to induce photoisomerization in both *Z* to *E* and *E* to *Z* directions by visible light. HTIs also show moderate photochromicity, with a bathochromically shifted absorption of the *E* isomer (typically 20–30 nm). This photochromicity permits to accumulate the respective isomer in high yields (up to 95%) after continuous irradiation, despite comparatively low quantum yields for the photoisomerization ($\eta_{Z/E}$ = 14–23%, $\eta_{E/Z}$ = 5–33%). Taken together with highly fatigue resistant photoswitching and the aforementioned enhanced thermal bistability, these favorable photophysical properties render HTIs into very interesting candidates especially for biological and material science applications.

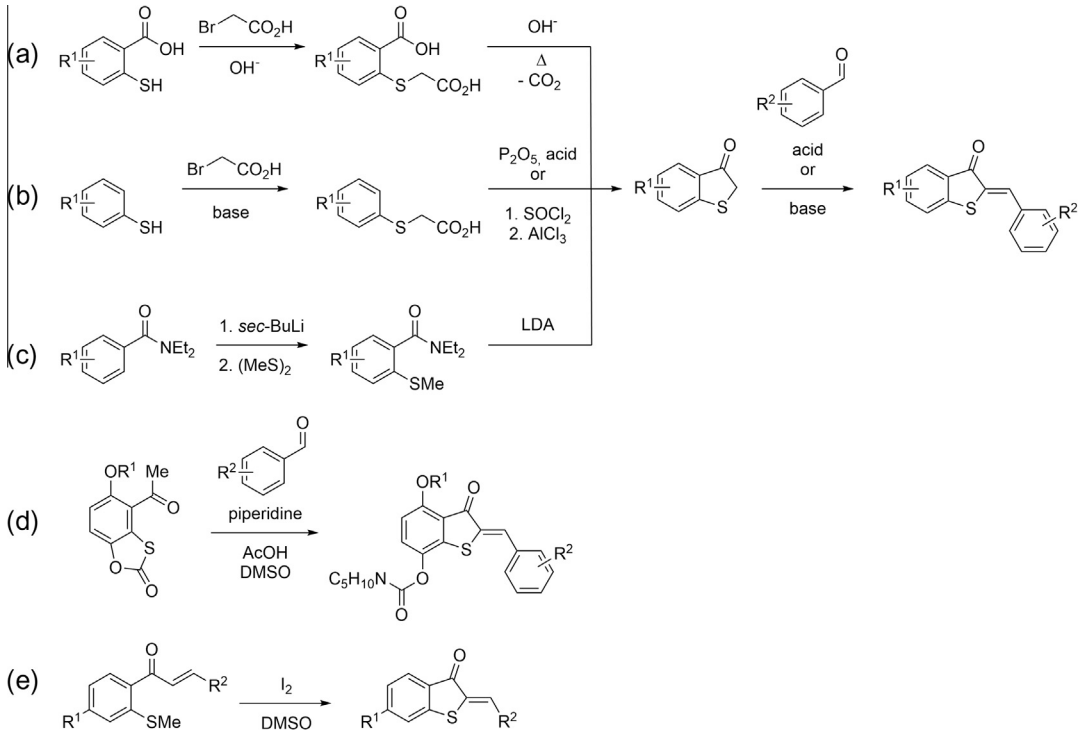
Synthesis of HTIs

The synthesis of HTIs is well developed nowadays and a variety of routes are available since their discovery. The different syntheses of HTIs have been thoroughly reviewed,[28] therefore we just describe the most commonly used ones in Scheme 1. Friedländer, who described HTIs for the first time in 1906,[29] developed the earliest synthesis via a condensation reaction of benzothiophenone and benzaldehydes. The benzothiophenone ring was formed by an intramolecular condensation reaction of 2-[(carboxymethyl) thio]benzoic acid, which was in turn derived from thiosalicylic acid. Nowadays, the benzothiophenone is typically generated by intramolecular Friedel–Crafts acylation of 2-(phenylthio)acetic acid[30] or the corresponding acid chlorides.[31] Another route developed by Mukherjee et al. uses deprotonation of a methylthio group in the *ortho*-position of benzamides followed by instant ring closure.[32] This reaction was extended to a one-pot procedure by Cabiddu using benzoates instead of benzamides.[33] The condensation reaction with aldehydes as the last step of the synthesis can be performed under acidic or basic conditions, both of which are used frequently.

In 2005 Konieczny et al. reported a new domino reaction for the one pot synthesis of HTIs via 4-acetyl-2-oxo-benz[1,3]oxathiole.[34] In 2014 the group of Wang reported on iodine-mediated HTI formation using *ortho*-methylthiophenyl vinyl ketones.[35]

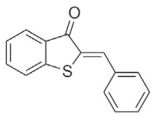
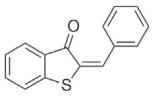
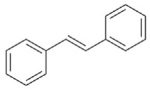
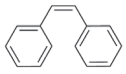
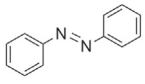
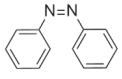
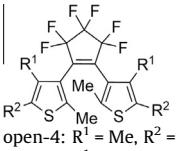
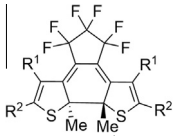
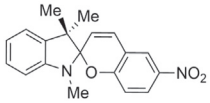
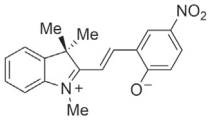
Photophysical properties of HTIs and photoisomerization mechanism

As stated above, the *Z* configuration of the HTI double bond is the thermodynamically stable form, while the *E* configuration is metastable and thermally isomerizes back to the *Z* configuration.[36] The energetic barrier for this process is 31.4 kcal/mol for unsubstitued HTI **1** in toluene solution, but changes with the introduction of substituents. Both, *Z* and *E* isomers have high extinctions (ε >20,000) in the visible region of the spectrum (λ_{max} >400 nm). The absorption spectrum of the *E* isomer shows a moderate bathochromic shift of about 24 nm, resulting in a rather small photochromicity of HTIs.[37] Upon irradiation of the *Z* isomer with



Scheme 1. Most commonly used syntheses of HTI photoswitches (a)–(c). The thermodynamically stable *Z* isomers are shown. (a) Friedländers original synthesis; (b) the most common access to the benzothiophenone ring by intramolecular Friedel–Crafts acylation; (c) Mukherjee et al. developed a very mild synthesis via *ortho*-lithiation chemistry followed by LDA induced ring closure. This method provides a very wide functional-group tolerance. Two more recent developments—a domino reaction (d) and an iodine mediated route (e) are also shown.

Table 1
Comparison of the physical and photophysical properties of HTI with common photoswitches

Compound	Extinction λ_{max} in nm (ε in L mol^{-1} cm^{-1})	Isomer yield in pss (at irradiation λ in solvent)	Quantum yield ϕ	Life time of excited state τ in ps	Activation barrier of thermal E to Z isomerization in kcal·mol^{-1}
Hemithioindigo[9]					
 *Z*-**1**	433 (12,600), 328 (17,000), 315 (19,800) in CH_2Cl_2	94% *E* (420 nm in CH_2Cl_2)	$\phi_{Z/E}$ = 0.23 in CH_2Cl_2	$\tau_{Z/E}$ = 38 in CH_2Cl_2	
 *E*-**1**	457 (5600), 321 (13,500) in CH_2Cl_2	100% *Z* (505 nm in CH_2Cl_2)	$\phi_{E/Z}$ = 0.05 in CH_2Cl_2	$\tau_{E/Z}$ = 23 in CH_2Cl_2	ΔG^* = 31 in toluene
Stilbene					
 *trans*-**2**	294 (27,600) in ethanol[10]	91% *cis* (in benzene)[11]	$\phi_{trans/cis}$ $\pi \rightarrow \pi^*$ = 0.52 in hexane[12]	τ_{trans} = 75 in *n*-hexane[13]	
 *cis*-**2**	278 (9800) in ethanol[10]		$\phi_{trans/cis}$ = 0.35 in hexane[12]	τ_{cis} = 1.05 in *n*-hexane[14]	E_a = 43 in *tert*-butylbenzene[15]
Azobenzene					
 *trans*-**3**	320 (21,300), 443 (500) in ethanol[16]	90% *cis* (317 nm in benzene)[17]	$\phi_{trans/cis}$ $\pi \rightarrow \pi^*$ = 0.11 $n \rightarrow \pi^*$ = 0.25 in *n*-hexane[3]	τ_{trans} = 0.32; 2.1 in ethanol[18]	
 *cis*-**3**	281 (5300), 432 (23,100) in ethanol[16]		$\phi_{cis/trans}$ $\pi \rightarrow \pi^*$ = 0.44 $n \rightarrow \pi^*$ = 0.56 in *n*-hexane[3]	τ_{cis} = 0.17; 2.0 in ethanol[18]	E_a = 23 in *n*-heptane[19]
Dithienylethene					
 open-4: R^1 = Me, R^2 = H open-5: R^1 = H, R^2 = Me	**4**: 234 (13,000) in hexane[20]	**4**: 62% closed (313 nm in hexane)[21]	**4**: ϕ = 0.21[20]	**5**: 12 ring closure in cyclohexane[22]	
 close-**4**: R^1 = Me, R^2 = H close-**5**: R^1 = H, R^2 = Me	**4**: 534 (5000) in hexane[20]		**4**: ϕ = 0.13 in hexane[20]		**4**: stable (lifetime longer than 12 h at 80 °C)[23]
Spiropyran					
 spiropyran-**6**	298 (8570) in ethanol[24]	100% merocyanin (334 nm in THF)[25]	ϕ_{Sp} = 0.15 in ethanol[24]	τ = 67 (λ_{exc} = 630 nm), 36 (λ_{exc} = 490 nm) in toluene[26]	
 merocyanin-**6**	537 (36,800) in ethanol[24]		ϕ_{Mc} = 0.04 in ethanol[24]		ΔG^* = 22 in DMSO[27]

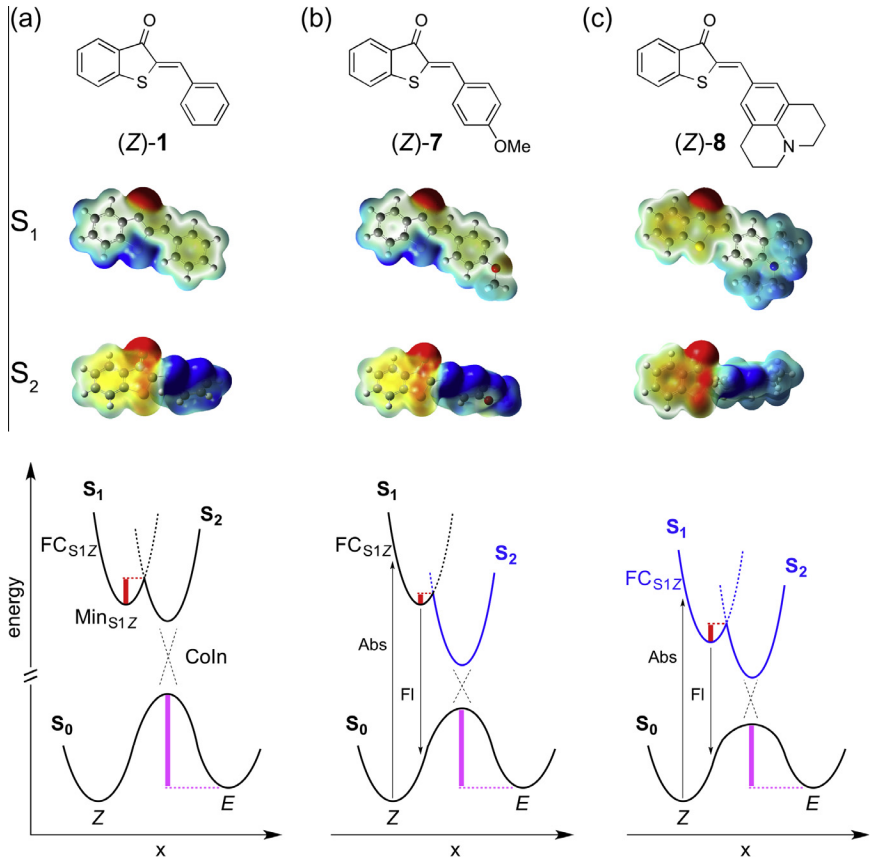


Figure 2. Mechanism of the photoisomerization of the *Z* isomers of (a) unsubstitued HTI **1**, (b) methoxy-substituted HTI **7**, and (c) the julolidine derivative HTI **8**. The polarization of each derivative in the S_1 and S_2 excited state is given in color code. Red bars indicate the energy barrier heights in the excited state responsible for the rate of photoisomerization. Purple bars indicate energy barrier heights in the ground state responsible for the rate of thermal *E*/*Z* isomerization. Weak donor substituents (i.e., methoxy in HTI **7**) lead to increase of both, photoisomerization and thermal isomerization rates. Strong donors (i.e., julolidine in HTI **8**) lead to a decrease in photoisomerization rate and an increase in the thermal isomerization rate.

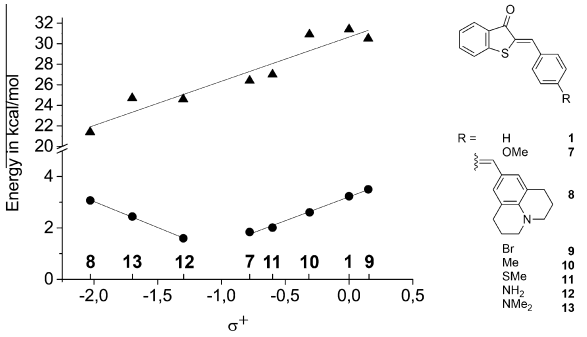


Figure 3. Hammett correlation between the electron donor capacity (σ^+ constant) of a *para*-substituent at the stilbene fragment of HTIs **1**, **7**–**13** and the energy barrier for *Z*/*E* photoisomerization (●) and thermal *E*/*Z* isomerization (▲). In the ground state increasing donor capacity leads to faster thermal *E*/*Z* isomerization. In the excited state a limit for the lowest barrier, that is, the highest rate of the photoisomerization is found at a σ^+ constant of −1.1.

blue light (typically 420 nm) *Z*/*E* photoisomerization takes place, which was first shown by Mostoslavskii and co-workers in 1961.[36b] His assignment of the two isomeric structures, with the *Z* isomer being the thermodynamically stable isomer and the *E* isomer being its photoproduct, was confirmed in 1977 by Reamonn and O'Sullivan using an intramolecular cyclization reaction and NMR spectroscopy.[36a] In the early 1990s Ichimura et al. showed that the photoisomerization of HTIs is also highly fatigue resistant, and can be repeated many thousand times before deterioration of the dye.[38]

The photoisomerization of unsubstituted HTI **1** is a very fast process, and takes about 38 ps with a quantum yield of 12% (in CH_2Cl_2 as solvent).[9,39] The reverse *E*/*Z* photoisomerization is initiated by light with longer wavelengths (typically >500 nm) and proceeds faster (23 ps) but with a lower quantum yield (5%).[9] This is due to another radiationless deexcitation channel of the *E* isomer, which does not lead to isomerization. Because of the extremely fast photoisomerization of HTIs, competing radiative deexcitation processes such as fluorescence or phosphorescence are usually not seen to an appreciable amount. Today, a detailed mechanistic understanding of the photoisomerization processes of HTIs is available. Many insights have been gained by the use of ultrafast spectroscopies, for example, time-resolved absorption,[40] fluorescence, and IR or Raman spectroscopy,[3,5b-e,5g] which allow to investigate fast photochemical reactions on very short (fs or ps) time scales. Seminal studies of the ultrafast behavior of HTIs upon photoexcitation were carried out by the groups of Zinth and Rück-Braun[39,41] and a thorough theoretical description of the excited state of unsubstituted HTI **1** by de Vivie-Riedle and co-workers.[42] Earlier theoretical descriptions have been given by the groups of Ganguly[43] and Plötner.[44]

In a simplified picture (Fig. 2a), the excited state potential energy surface of photoexcited HTI is a combination of two (S_1 and S_2) excited states, which mix at a certain geometry point. This point is close to a 90° rotation of the central double bond. The mixing of the S_1 and S_2 excited states creates a barrier, which

determines the speed of the *Z*/*E* photoisomerization. After the barrier a conical intersection (CoIn) is present, connecting the excited and the ground state at 90° rotation of the central double bond. The residual 90° rotation takes place at the ground state (S_0) potential energy surface resulting in the formation of either the *E* or the *Z* isomer. The mechanistic details of the photoisomerization process are depicted in Fig. 2a for unsubstituted HTI **1** and are explained in the following. Photoexcitation of the *Z* isomer in the ground state (S_0) leads to population of the Franck–Condon region (FC_{S1Z}), which is left quickly (2–4 ps) to reach a local minimum (Min_{S1Z}) with a 'vertical' (relative to the molecules long axis) polarization of the molecule. In this polarized state the sulfur atom of the thioindigo fragment is highly electron deficient, while the carbonyl oxygen atom gains significant electron density. This polarization has been associated with the long-wavelength band of HTI absorption as early as 1976 by Yugai and Mostoslavskii.[45] At the barrier in the excited state, the polarization changes to a 'horizontal' (relative to the molecules long axis) polarization, where the stilbene fragment is electron deficient, the sulfur atom is neutral, and the carbonyl oxygen still retains high electron density. This 'horizontal' polarization is lost during transit through the CoIn and a more biradical-like character is formed at 90° rotation of the central double bond back in the ground state. After excitation of the *E* isomer a similar photoisomerization mechanism is followed with similar polarizations[46] along the way, but with one important difference. In the S_1 excited state of the *E* isomer, a virtually barrier-less transition from the excited state to the ground state is found in the theoretical description,[42] which takes place before isomerization of the double bond has occured. This nonradiative 'loss channel' is responsible for the low quantum yield of the *E*/*Z* photoisomerization as well as the faster deexcitation and very small fluorescence that is observed for the *E* isomer.

Substituents strongly affect the physical, photophysical, and photoisomerization[47] characteristics of HTIs and—given a thorough mechanistic understanding—can be used to design HTIs with new and interesting properties. A simple, but helpful approach to understand substituent effects is the description of HTI in terms of a donor–acceptor substituted double bond. The thioindigo fragment with its carbonyl group can be regarded as the acceptor moiety, while the stilbene fragment would serve as the donor moiety in this picture. If the donor capacity of the stilbene fragment is enhanced by introduction of electron donor-substituents, the donor–acceptor character of the central double bond and therefore conjugation across that bond is increased. This leads to known effects of red-shifted absorption and increased extinction, while at the same time the thermal back isomerization is accelerated. The latter finding can readily be explained by partial loss of double bond character because of the increased conjugation.

In order to gain deeper insights into the origins of physical properties, series of substituted derivatives can be studied and analyzed according to Hammett relationships (Fig. 3). In such a series of HTIs bearing increasingly strong electron donor-groups at the stilbene fragment, a similar trend is seen for the excited state and ground state rates of isomerization. The stronger the donor substituent becomes, the faster is the rate of both, the photoisomerization (excited state kinetics) as well as the thermal *E*/*Z* isomerization (ground state kinetics) as shown in Figure 2b.[9,41b] The trend seen for the excited state kinetics can be explained by different stabilization of the two mixing excited states (S_1 and S_2). While the 'vertical' polarization of the S_1 state cannot be stabilized by the donor substituents of the stilbene fragment, the S_2 state is significantly stabilized. Therefore the mixing point of the S_1 and S_2 is shifted and a smaller barrier—that is, faster photoisomerization—results. However, we recently found that this mechanism only holds, if the donor strength of the substituent is not very large. In a collaborative approach with the groups of Zinth and de Vivie-Riedle, we studied a series of HTIs with very strong donors and observed an opposite Hammett correlation in the excited state (Fig. 3). Now, increasing donor strength led to slower photoisomerization. We could explain this finding in terms of a change of the polarization in the excited S_1 state and concomitant stabilization of both, the S_1 and S_2 excited states by very strong donor substituents at the stilbene fragment (Fig. 2c).[9] The S_1 state stabilization was readily probed by measuring the stationary absorption and fluorescence energies, which showed significant effects only for very strong donor substituents. We thus discovered and quantified a principal limit for the photoisomerization rate of HTIs, the maximum of which (excited state lifetime of 1.1 ps for the *Z* and 0.6 ps for the *E* isomer) should occur for a donor substituent with a Hammett σ^+ constant of about −1.1.

Substituents at the thioindigo fragment can also have strong effects on the photoisomerization kinetics. Especially the *para*-position of the sulfur atom is sensitive, as donor substituents in this position lead to a notable decrease in photoisomerization speed.[39] A mechanistic explanation for this behavior has yet to be given.

Applications of HTI photoswitches

To be useful for applications photoswitches must meet a variety of special requirements: (i) the dyes should be photochromic, meaning that the absorption spectra of the different isomers do not overlap completely; (ii) irradiation with light should produce a specific and distinct change of the molecule, for example, isomerization, pericyclic reaction, or tautomerization; (iii) the switching process must be reversible and highly fatigue resistant in either direction; (iv) the quantum yields of the induced photoreactions should be high; (v) the absorption wavelengths should not overlap with other components of the particular system that has to be switched, so that the photoswitch can selectively be irradiated; (vi) the thermal relaxation rates should be small; and (vii) the reaction rate of the photoinduced process should be fast to prevent competing side-reactions that also lead to deexcitation (fluorescence, phosphorescence, unproductive relaxations to the ground state). HTIs meet most of the above requirements, but especially important is their absorption in the visible region for both isomeric states while maintaining a high thermal stability of the metastable *E* isomer. Because of these particular properties, HTIs are intrinsically highly attractive for biological and material science applications. It is therefore somewhat surprising, that the first applications of HTIs as truly molecular photoswitches (i.e., not as simple photochromic components in, for example, sunscreening, photographic or optical recording materials) started to emerge only in the 1990s. In 1992 Seki et al. implemented amphiphilic groups into HTIs **14**–**16** and studied the photochromism in bilayer membranes, to affect changes of membrane properties in response to irradiation (Fig. 4a).[38c] About ten years later, in 2001 the group of Fyles reported HTI-based photoswitchable lipids (**17**–**20**) and showed reversible switching within phosphatidylserine vesicles (Fig. 4b).[48]

Although the small geometrical changes induced by photoisomerization of HTIs could be an actual advantage for lipid- and liquid-crystal related applications, this approach has not been followed up since. One problem that could be responsible for this hesitation is the possibility of side reactions (Scheme 2) that are observed sometimes under irradiation.[49] If the *ortho*-positions of the stilbene fragment are substituted with halides such as fluorine, an irreversible intramolecular cyclization takes place after photoinduced *Z*/*E* isomerization.[50] Another side reaction that can compete with photoisomerization is the light-induced intermolecular [2+2] cycloaddition of the central double bond.[38c,51] This side

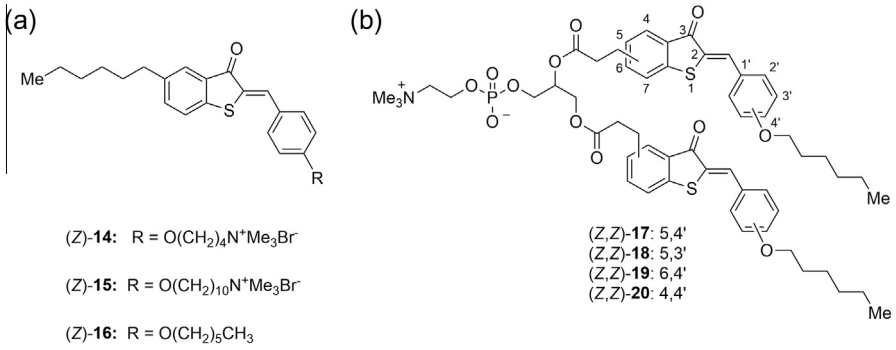
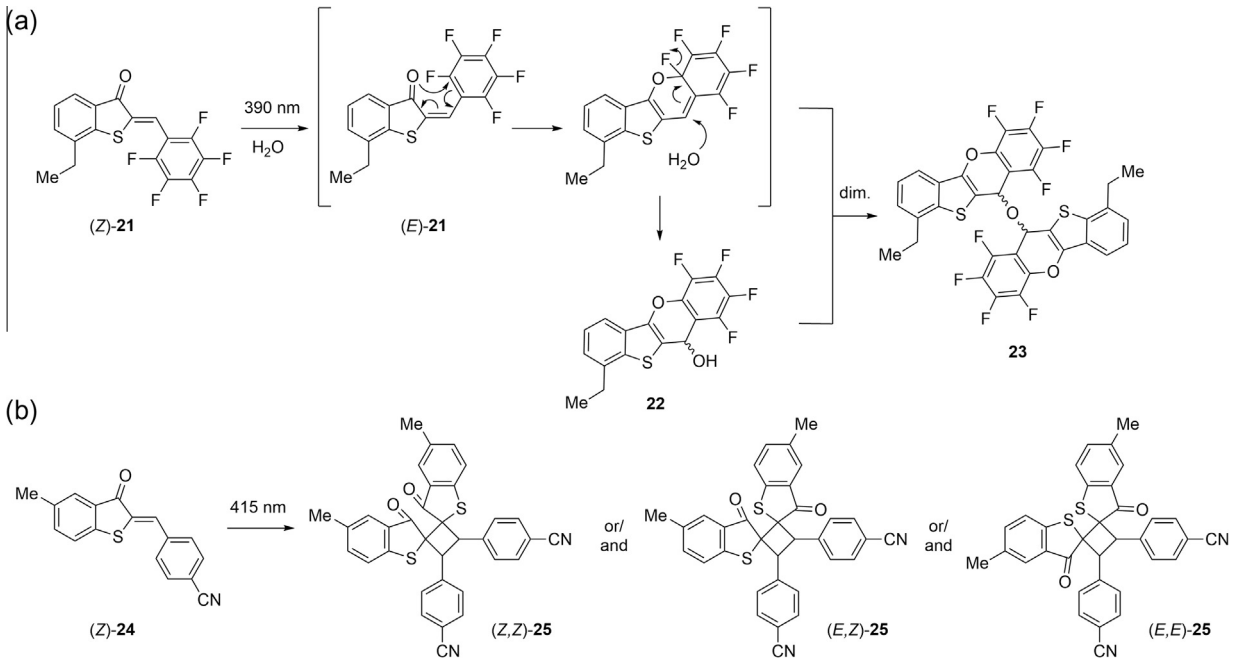


Figure 4. Early examples of functional HTI photoswitches: (a) HTI amphiphiles for photoswitching in bilayer membranes[38c] and (b) HTI based photoswitchable lipids.[48]



Scheme 2. Side reactions of HTI photoisomerization (a) intramolecular cyclization after *Z*/*E* photoisomerization followed by H_2O trapping or dimerization (dim.), (b) [2+2] cycloaddition with different possible stereochemical outcomes.

reaction is especially important if HTI concentrations are very high or clustering of HTIs takes place, for example by hydrophobic interactions in aqueous medium. Interestingly, a similar light induced but thermally reversible [2+2] cycloaddition of the central double bond can actually be used as a new photoswitching process for benzoyl-HTIs.[52]

In 2004 the groups of Woolley and Rück-Braun reported on a HTI-based amino acid, which was incorporated into gramicidin ion channels and could be used to modulate the ion current by photoisomerization in a predictable way.[53] This was the first truly biological application of HTIs, proving that this photoswitch is suitable for applications in aqueous medium in the presence of a complex environment.

Rück-Braun and co-workers were also the first to prepare a number of HTI-based amino acids[54] and peptides[41a,55] and the photoisomerization kinetics of these compounds were studied in collaboration with Zinth and co-workers.[41a,55,56] It was shown, that the photoisomerization in aqueous medium is also a very fast process, which efficiently competes with fluorescence or phosphorescence deexcitation pathways. In 2008 Gogoll and co-workers adapted these syntheses to generate HTI-based photomodulable peptide switches.[57] Two HTI-containing peptides were used recently by Rück-Braun and Zinth to induce changes in peptide secondary-structures via irradiation with visible light.[58] These structural changes were monitored using ultrafast spectroscopy in the visible and the infrared region of the spectrum. The authors demonstrated that the photoisomerization of incorporated HTIs proceeds slower than the photoisomerization of the isolated HTI chromophores by a factor of 2.0–4.6. If the HTI was incorporated into a β-hairpin structure, photoisomerization did not only lead to instant changes of the peptide structure but also long term changes were observed on a timescale of ns (Fig. 5a). These changes were interpreted as subsequent rearrangements and loss of hydrogen bonds within the β-hairpin in order to reach the final equilibrium structure with *E* isomeric HTI. Here the great potential of the relatively low energy-input upon photoirradiation was used effectively to 'mildly' initialize large structural changes in peptides. These findings open up exciting future prospectives for the manipulation of biological functions associated with secondary structure changes of peptides and proteins using HTI photoswitches and visible light. Related studies in cyclic, HTI-incorporating peptides by the group of Gogoll were less successful, as both *Z* and *E* isomeric forms did not allow a stable secondary structure to be formed.[59] These findings underline the fact that careful design

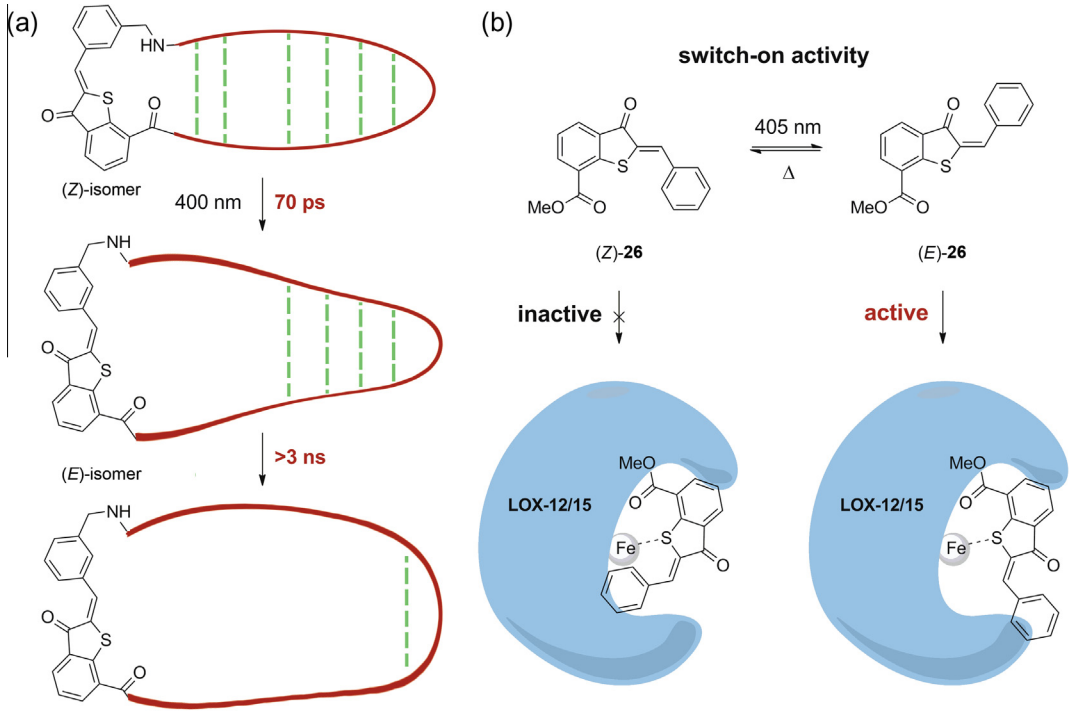


Figure 5. Biological applications of HTI photoswitches. (a) HTI modified β-hairpin peptide, which forms multiple hydrogen bonds. After photoisomerization of the HTI to its *E* configuration, instant loss of hydrogen bonds in the vicinity of the HTI takes place. This instant structural response of the peptide is followed by long term changes on the ns time scale.[58] (b) HTI **26** serves as photoinducible inhibitor of the lipoxygenase LOX-12/15. While the thermodynamically stable *Z* isomer has only very low affinity for the enzyme, the *E* isomer binds strongly.[60]

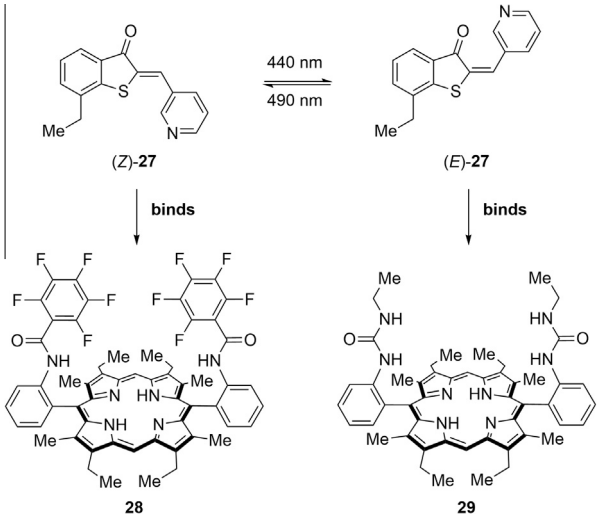


Figure 6. HTI based supramolecular shuttle. HTI **27** is more strongly bound by porphyrin receptor **28** in its *Z* isomeric state. Upon photoisomerization of **27** the *E* isomer is formed, which is more strongly bound by porphyrin receptor **29**.[63]

and analysis of the particular biological system and its geometrical demands are essential to efficiently apply the rather rigid HTI photoswitches.

The groups of Kuhn and Rück-Braun have provided yet another biological application of HTIs using them as photoswitchable inhibitors of the lipid-peroxidizing lipoxygenases (LOXs).[60] These enzymes are involved in a variety of biological processes and diseases for example inflammatory diseases, asthma, cell maturation, or atherosclerosis, and osteoporosis. Based on structural similarity of ebselen,[61] a known inhibitor for LOX-12/15,[62] and the *E* isomeric form of HTI **26** a photoswitchable LOX-enzyme inhibition was studied with the latter (Fig. 5b). At first a moderate photoswitching efficiency was observed for HTI **26** in DMSO, where 62% of the *E* isomeric form could be accumulated in the photostationary state (pss) using 405 nm light. Since the metastable *E* isomeric form is the biologically active form, HTI **26** constitutes a 'switch-on' inhibitor and a quantitative conversion from *Z* to *E* is not required to observe effective modulation of biological functions. What is required for such modulation however, is a very different inhibition capacity of the *Z* and the *E* isomer of the HTI inhibitor. Therefore, the two isomers were separated via HPLC and each subjected to oxygraphic enzyme inhibition assays. The high thermal stability of the metastable *E* isomer of HTI photoswitches is truly advantageous in this regard, as it conveniently allows assessing the biological activity of each isomer directly without the need to extrapolate binding constants from the pss. Three LOX-enzymes were investigated as targets for photoswitchable inhibition, the native and recombinant forms of LOX-12/15 as well as the Ile418Ala mutant. In vitro the *E* isomer of HTI **26** displayed an up to 33 fold greater inhibition compared to the *Z* isomer. A considerably higher potency of the *E* isomer versus the *Z* isomer was even demonstrated intracellularly. These findings are pharmacologically very appealing, particularly for the local treatment of skin inflammation and the reduction of side effects and dosage.

The first supramolecular application of HTIs was published by Tanaka et al. in 2008, where an effective, light induced shuttling of the *Z* and *E* isomeric forms of HTI **27** between two different, porphyrin-based receptors was demonstrated (Fig. 6).[63] Such shuttling constitutes a significantly more complex process than the simpler 'catch and release' that is typically controlled via photoisomerizations. The authors then went one step further and used the photoinduced affinity change of the HTI to control a secondary process, the binding of *p*-benzoquinone to each of the two receptors. The same group also reported on benzoyl-extended HTIs, which were used as light-responsive molecular switches to control porphyrin-quinone recognition.[64]

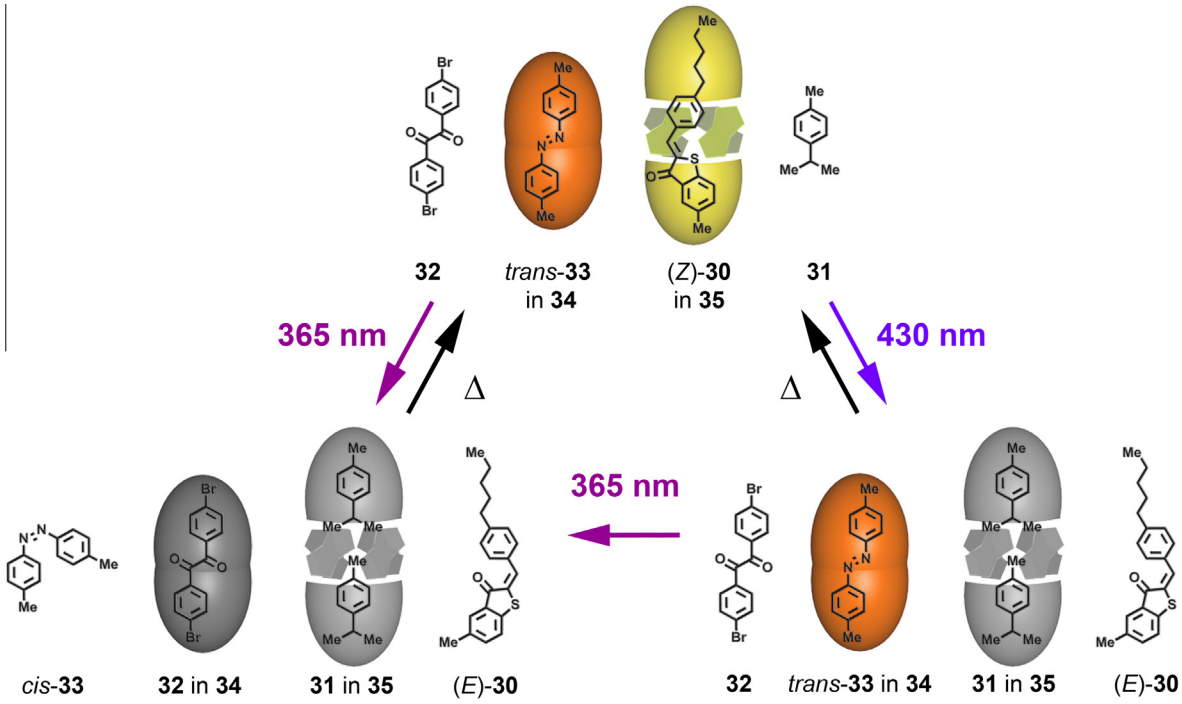


Figure 7. Sequential control over the state of encapsulation using two photoswitches in two differently sized molecular capsules. The *Z* isomer of the larger HTI **30** is readily accommodated within the expanded molecular capsule **35** (yellow) and the smaller *trans*-4,4′-dimethylazobenzene (*trans*-**33**) is readily accommodated within the smaller dimeric capsule **34** (red). Irradiation with 430 nm light leads to selective photoisomerization of only **30** and concomitant guest exchange in the larger capsule **35**. Subsequent irradiation with 365 nm light leads to photoisomerization of the azobenzene *trans*-**33** followed by guest exchange in the smaller capsule **34**. A heating step restores the initial state of the system.

Dube and Rebek Jr. reported on another supramolecular application of HTI photoswitches, which aimed at expanding the level of molecular complexity that can be controlled by light irradiation.[65] Most applications of photoswitches focus on using a single switch and associate two different properties with each accessible isomeric form. Only very recently have multiple, orthogonal photoswitches that can be irradiated at different wavelengths become investigated[66] and applied.[67] Because of their distinct absorption in the visible range of the spectrum HTI photoswitches are well suited for the combination with other photoswitches, which mostly absorb in the UV region. In this study, an azobenzene was used together with an alkyl-substituted HTI to selectively affect guest exchange in molecular capsules (Fig. 7). Two molecular capsules with different sizes were assembled in mesitylene solution in the presence of the *Z* isomer of HTI **30**, *p*-cymene (**31**), 4,4′-dibromobenzil (**32**), and *trans*-4,4′-dimethylazobenzene (*trans*-**33**). Because of considerably higher affinity *trans*-**33** was taken up by the smaller dimeric capsule **34** and the *Z* isomer of HTI **30** was taken up by the larger expanded capsule **35**, while cymene **31** and benzil **32** remained in solution. Irradiation with 430 nm induced photoisomerization of HTI **30** but did not have any effect on the encapsulated azobenzene *trans*-**33**. The resulting *E* isomer of HTI **30** has a bent geometry that cannot be bound by the larger capsule **35**. Therefore, a guest exchange takes place solely in this capsule and two molecules of *p*-cymene (**31**) are taken up. After completion of this first guest exchange, a second guest exchange in the smaller dimeric capsule (**34**) could be affected by irradiation with 365 nm light. Now the azobenzene *trans*-**33** is photoisomerized into its *cis*-configuration and cannot be accommodated inside the molecular capsule **34** anymore. The weaker binding benzil guest **32** is now the only suitable guest left for the smaller capsule and is therefore taken up. A heating step reverses the whole system to the starting point. With three different inputs, 430 nm, 365 nm, and heating three different states of the supramolecular assembly can be conveniently and reversibly accessed in solution. This constitutes the most complex control of supramolecular encapsulation known to date. The study also demonstrated that significant geometrical differences between the *Z* and E isomers can be realized if HTI is substituted appropriately.

Conclusion

In summary, the development of HTIs as alternative photoswitching systems is an important and rapidly growing field, as these photoswitches offer a variety of advantageous physical and photophysical properties compared to traditional photoswitches. Especially the combination of red shifted absorption and high thermal stability of the metastable *E* isomeric state renders HTIs into very valuable alternatives to azobenzenes, dithienylethenes, or spiropyranes. With HTIs UV irradiation can be replaced by less stressful visible light to exert photocontrol in a molecular system and HTIs can easily be combined with other photoswitches to implement selective and possibly orthogonal photocontrol.

Although the mechanistic origins of many physical and photophysical properties are well understood nowadays, very interesting and unique properties can be expected from new substitution patterns that have not as of yet been scrutinized. A thorough mechanistic understanding of the photoisomerization mechanism and the effects of different substituents, solvents, and chemical surrounding will ultimately enable a rational design approach to tailor HTI properties to specific applications in the future. Emerging applications of HTIs show already the great potential of these photoswitches to control molecular processes in material sciences as well as biological and supramolecular chemistry. We expect great progress in this young and exciting field where new applications and unusual properties will be realized thus, establishing HTIs as distinct and highly valuable phototools.

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References and notes

1. (a) Russew, M. M.; Hecht, S. *Adv. Mater.* **2010**, *22*, 3348–3360; (b) Eelkema, R.; Pollard, M. M.; Vicario, J.; Katsonis, N.; Ramon, B. S.; Bastiaansen, C. W.; Broer, D. J.; Feringa, B. L. *Nature* **2006**, *440*, 163; (c) Venkataramani, S.; Jana, U.; Dommaschk, M.; Sonnichsen, F. D.; Tuczek, F.; Herges, R. *Science* **2011**, *331*, 445–448; (d) Ohara, H.; Morimoto, M.; Irie, M. *Photochem. Photobiol. Sci.* **2010**, *9*, 1079–1081.
2. (a) Velema, W. A.; Szymanski, W.; Feringa, B. L. *J. Am. Chem. Soc.* **2014**, *136*, 2178–2191; (b) Fehrentz, T.; Schonberger, M.; Trauner, D. *Angew. Chem., Int. Ed.* **2011**, *50*, 12156–12182; (c) Janovjak, H.; Szobota, S.; Wyart, C.; Trauner, D.; Isacoff, E. Y. *Nat. Neurosci.* **2010**, *13*, 1027–1032.
3. Bandara, H. M.; Burdette, S. C. *Chem. Soc. Rev.* **2012**, *41*, 1809–1825.
4. (a) Saltiel, J.; Megarity, E. D.; Kneipp, K. G. *J. Am. Chem. Soc.* **1966**, *88*, 2336–2338; (b) Waldeck, D. H. *Chem. Rev.* **1991**, *91*, 415–436; (c) Waldeck, D. H. *J. Mol. Liq.* **1993**, *57*, 127–148.
5. Lukyanov, B. S.; Lukyanova, M. B. *Chem. Heterocycl. Compd.* **2005**, *41*, 281–311.
6. Irie, M. *Phosphorus Sulfur Silicon Relat. Elem.* **1997**, *120*, 95–106.
7. (a) Asano, T.; Okada, T.; Shinkai, S.; Shigematsu, K.; Kusano, Y.; Manabe, O. *J. Am. Chem. Soc.* **1981**, *103*, 5161–5165; (b) De Maria, P.; Fontana, A.; Gasbarri, C.; Siani, G.; Zanirato, P. *ARKIVOC* **2009**, *viii*, 16–29; (c) Wazzan, N. A.; Richardson, P. R.; Jones, A. C. *Photochem. Photobiol. Sci.* **2010**, *9*, 968–974.
8. (a) Beharry, A. A.; Sadovski, O.; Woolley, G. A. *J. Am. Chem. Soc.* **2011**, *133*, 19684–19687; (b) Samanta, S.; Beharry, A. A.; Sadovski, O.; McCormick, T. M.; Babalhavaeji, A.; Tropepe, V.; Woolley, G. A. *J. Am. Chem. Soc.* **2013**, *135*, 9777–9784; (c) Bleger, D.; Schwarz, J.; Brouwer, A. M.; Hecht, S. *J. Am. Chem. Soc.* **2012**, *134*, 20597–20600.
9. Maerz, B.; Wiedbrauk, S.; Oesterling, S.; Samoylova, E.; Nenov, A.; Mayer, P.; de Vivie-Riedle, R.; Zinth, W.; Dube, H. *Chem. Eur. J.* **2014**, *20*, 13984–13992.
10. Suzuki, H. *Bull. Chem. Soc. Jpn.* **1952**, *25*, 145–150.
11. Syamala, M. S.; Devanathan, S.; Ramamurthy, V. *J. Photochem.* **1986**, *34*, 219–229.
12. Rodier, J.-M.; Myers, A. B. *J. Am. Chem. Soc.* **1993**, *115*, 10791–10795.
13. Courtney, S. H.; Kim, S. K.; Canonica, S.; Fleming, G. R. *J. Chem. Soc., Faraday Trans.* **1986**, *2*, 2065–2072.
14. Rice, J. K.; Baronavski, A. P. *J. Phys. Chem.* **1992**, *96*, 3359–3366.
15. Meier, H. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1399–1420.
16. Birnbaum, P. P.; Linford, J. H.; Style, D. W. G. *Trans. Faraday Soc.* **1953**, *49*, 735–744.
17. Bortolus, P.; Monti, S. *J. Phys. Chem.* **1979**, *83*, 648–652.
18. Naegele, R.; Hoche, R.; Zinth, W.; Wachtveitl, J. *Chem. Phys. Lett.* **1997**, *272*, 489–495.
19. Brown, E. V.; Granneman, G. R. *J. Am. Chem. Soc.* **1975**, *97*, 621–627.
20. Uchida, K.; Irie, M. *Chem. Lett.* **1995**, *24*, 969–970.
21. Irie, M.; Sakemura, K.; Okinaka, M.; Uchida, K. *J. Org. Chem.* **1995**, *60*, 8305–8309.
22. Miyasaka, H.; Nobuto, T.; Itaya, A.; Tamai, N.; Irie, M. *Chem. Phys. Lett.* **1997**, *269*, 281–285.
23. Irie, M. *Chem. Rev.* **2000**, *100*, 1685–1716.
24. Santos, C. S.; Miller, A. C.; Pace, T. C.; Morimitsu, K.; Bohne, C. *Langmuir* **2014**, *30*, 11319–11328.
25. Jukes, R. T. F.; Bozic, B.; Hartl, F.; Belser, P.; De Cola, L. *Inorg. Chem.* **2006**, *45*, 8326–8341.
26. Wohl, C. J.; Kuciauskas, D. *J. Phys. Chem. B* **2005**, *109*, 22186–22191.
27. Kießwetter, R.; Pustet, N.; Brandl, F.; Mannschreck, A. *Tetrahedron: Asymmetry* **1999**, *10*, 4677–4687.
28. Konieczny, M. T.; Konieczny, W. *Heterocycles* **2005**, *65*, 451–464.
29. Friedländer, P. *Chem. Ber.* **1906**, *39*, 1060–1066.
30. (a) Friedländer, P.; Vorozhtzov, N. N. *Justus Liebigs Ann. Chem.* **1912**, *388*, 1–23; (b) Guha, S. K. *J. Indian Chem. Soc.* **1939**, *16*, 127–130.
31. (a) Auwers, K. V. *Ber. Dtsch. Chem. Ges. B* **1920**, *53B*, 2285–2299; (b) Dalgliesh, C. E.; Mann, F. G. *J. Chem. Soc.* **1945**, 893–909.
32. (a) Mukherjee, C.; De, A. *Synlett* **2002**, 325–327; (b) Kamila, S.; Mukherjee, C.; De, A. *Synlett* **2003**, 1479–1481.
33. Cabiddu, M. G.; Cabiddu, S.; Cadoni, E.; De Montis, S.; Fattuoni, C.; Melis, S.; Usai, M. *Synthesis* **2002**, 875–878.
34. Konieczny, M. T.; Konieczny, W.; Wolniewicz, S.; Wierzba, K.; Suda, Y.; Sowinski, P. *Tetrahedron* **2005**, *61*, 8648–8655.
35. Zheng, G.; Ma, X.; Liu, B.; Dong, Y.; Wang, M. *Adv. Synth. Catal.* **2014**, *356*, 743–748.
36. (a) Reamonn, L. S. S.; O'Sullivan, W. I. *J. Chem. Soc. Perkin Trans. 1* **1977**, 1009–1012; (b) Izmail'skii, V. A.; Mostoslavskii, M. A. *Ukr. Khem. Zh.* **1961**, *27*, 234–237.
37. (a) Mostoslavskii, M. A.; Izmail'skii, V. A.; Shapkina, M. M. *J. Gen. Chem. USSR* **1962**, *32*, 1731–1739; (b) Mostoslavskii, M. A.; Izmail'skii, V. A. *J. Gen. Chem. USSR* **1961**, *31*, 21–31; (c) Mostoslavskii, M. A.; Izmail'skii, V. A. *J. Gen. Chem. USSR* **1963**, *33*, 727–731; (d) Mostoslavskii, M. A.; Izmail'skii, V. A. *J. Gen. Chem. USSR* **1965**, *35*, 519–523.
38. (a) Ichimura, K.; Seki, T.; Tamaki, T.; Yamaguchi, T. *Chem. Lett.* **1990**, *9*, 1645–1646; (b) Yamaguchi, T.; Seki, T.; Tamaki, T.; Ichimura, K. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 649–656; (c) Seki, T.; Tamaki, T.; Yamaguchi, T.; Ichimura, K. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 657–663.
39. Cordes, T.; Schadendorf, T.; Rück-Braun, K.; Zinth, W. *Chem. Phys. Lett.* **2008**, *455*, 197–201.
40. Mukherjee, C.; Kamila, S.; De, A. *Tetrahedron* **2003**, *59*, 4767–4774.
41. (a) Cordes, T.; Weinrich, D.; Kempa, S.; Riesselmann, K.; Herre, S.; Hoppmann, C.; Rück-Braun, K.; Zinth, W. *Chem. Phys. Lett.* **2006**, *428*, 167–173; (b) Cordes, T.; Schadendorf, T.; Priewisch, B.; Rück-Braun, K.; Zinth, W. *J. Phys. Chem. A* **2008**, *112*, 581–588.
42. Nenov, A.; Cordes, T.; Herzog, T. T.; Zinth, W.; de Vivie-Riedle, R. *J. Phys. Chem. A* **2010**, *114*, 13016–13030.
43. Bhattacharya, S.; Pradhan, T. K.; De, A.; Chaudhury, S. R.; De, A. K.; Ganguly, T. *J. Phys. Chem. A* **2006**, *110*, 5665–5673.
44. Plötner, J.; Dreuw, A. *J. Phys. Chem. A* **2009**, *113*, 11882–11887.
45. (a) Yugai, G. A.; Mostoslavskii, M. A. *Khim. Geterotsikl. Soedin.* **1976**, 1032–1035; (b) Mostoslavskii, M. A.; Yugai, G. A. *Ukr. Khim. Zh. (Russ. Ed.)* **1976**, *42*, 1219–1222.
46. Yugai, G. A.; Mostoslavskii, M. A.; Paramonov, V. D. *Teor. Eksp. Khim.* **1976**, *12*, 700–704.
47. Cordes, T.; Schadendorf, T.; Lipp, M.; Rück-Braun, K.; Zinth, W. *Springer Ser. Chem. Phys.* **2009**, *92*, 319–321.
48. Eggers, K.; Fyles, T. M.; Montoya-Pelaez, P. J. *J. Org. Chem.* **2001**, *66*, 2966–2977.
49. Aoki, K.; Ichimura, K.; Tamaki, T.; Seki, T.; Kawanishi, Y. *Kobunshi Ronbunshu* **1990**, *47*, 771–777.
50. Tanaka, K.; Kohayakawa, K.; Irie, T.; Iwata, S.; Taguchi, K. *J. Fluorine Chem.* **2007**, *128*, 1094–1097.
51. T. Schadendorf, Ph.D. Thesis, Technical University Berlin 2008.
52. Tanaka, K.; Taguchi, K.; Iwata, S.; Irie, T. *Chem. Lett.* **2004**, *33*, 848–849.
53. Lougheed, T.; Borisenko, V.; Hennig, T.; Rück-Braun, K.; Woolley, G. A. *Org. Biomol. Chem.* **2004**, *2*, 2798–2801.
54. (a) Herre, S.; Steinle, W.; Rück-Braun, K. *Synthesis* **2005**, 3297–3300; (b) Schadendorf, T.; Hoppmann, C.; Rück-Braun, K. *Tetrahedron Lett.* **2007**, *48*, 9044–9047; (c) Steinle, W.; Rück-Braun, K. *J. Org. Lett.* **2003**, *5*, 141–144.
55. Cordes, T.; Riesselmann, K.; Herre, S.; Rück-Braun, K.; Zinth, W. *Springer Ser. Chem. Phys.* **2007**, *88*, 543–545.
56. (a) Cordes, T.; Heinz, B.; Regner, N.; Hoppmann, C.; Schrader, T. E.; Summerer, W.; Rück-Braun, K.; Zinth, W. *ChemPhysChem* **2007**, *8*, 1713–1721; (b) Cordes, T.; Elsner, C.; Herzog, T. T.; Hoppmann, C.; Schadendorf, T.; Summerer, W.; Rück-Braun, K.; Zinth, W. *Chem. Phys.* **2009**, *358*, 103–110.
57. Erdelyi, M.; Varedian, M.; Skold, C.; Niklasson, I. B.; Nurbo, J.; Persson, A.; Bergquist, J.; Gogoll, A. *Org. Biomol. Chem.* **2008**, *6*, 4356–4373.
58. Regner, N.; Herzog, T. T.; Haiser, K.; Hoppmann, C.; Beyermann, M.; Sauermann, J.; Engelhard, M.; Cordes, T.; Rück-Braun, K.; Zinth, W. *J. Phys. Chem. B* **2012**, *116*, 4181–4191.
59. Varedian, M.; Erdelyi, M.; Persson, A.; Gogoll, A. *J. Pept. Sci.* **2009**, *15*, 107–113.
60. Herre, S.; Schadendorf, T.; Ivanov, I.; Herrberger, C.; Steinle, W.; Rück-Braun, K.; Preissner, R.; Kuhn, H. *ChemBioChem* **2006**, *7*, 1089–1095.
61. Sies, H. *Methods Enzymol.* **1994**, *234*, 476–482.
62. (a) Walther, M.; Holzhütter, H.-G.; Kuban, R. J.; Wiesner, R.; Rathmann, J.; Kuehn, H. *Mol. Pharmacol.* **1999**, *56*, 196–203; (b) Minor, W.; Steczko, J.; Stec, B.; Otwinowski, Z.; Bolin, J. T.; Walter, R.; Axelrod, B. *Biochemistry* **1996**, *35*, 10687–10701.
63. Tanaka, K.; Kohayakawa, K.; Iwata, S.; Irie, T. *J. Org. Chem.* **2008**, *73*, 3768–3774.
64. Tanaka, K.; Taguchi, K.; Iwata, S.; Irie, T. *Supramol. Chem.* **2005**, *17*, 637–642.
65. Dube, H.; Rebek, J., Jr. *Angew. Chem., Int. Ed.* **2012**, *51*, 3207–3210.
66. Darwish, T. A.; Evans, R. A.; James, M.; Malic, N.; Triani, G.; Hanley, T. L. *J. Am. Chem. Soc.* **2010**, *132*, 10748–10755.
67. (a) Nishioka, H.; Liang, X.; Kato, T.; Asanuma, H. *Angew. Chem., Int. Ed.* **2012**, *51*, 1165–1168; (b) Gust, D.; Moore, T. A.; Moore, A. L. *Chem. Commun.* **2006**, 1169–1178; (c) Gust, D.; Andreasson, J.; Pischel, U.; Moore, T. A.; Moore, A. L. *Chem. Commun.* **2012**, 1947–1957; (d) Chen, W.-C.; Lee, Y.-W.; Chen, C.-T. *Org. Lett.* **2010**, *12*, 1472–1475.