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Photoswitchable General Base Catalysts*Philipp Viehmann and Stefan Hecht***Introduction and Background**

Chemists have recently started to control catalysts by external stimuli, such as ultrasound, electric fields, or light. Light is perhaps the most attractive means because of its inherently high spatiotemporal resolution. The concept of photoswitchable catalysts (Figure 1) involves light gating of the ground state reactivity of a given catalyst. This concept is in theory applicable to any thermal catalyst, provided a suitable light-gated photoreaction can influence the catalyst's activity and/or selectivity. The coupling of catalytic turnover of substrate molecules to an initial photoreaction leads to an overall amplification of the photon signal, that is, a quantum yield exceeding unity ($\Phi \geq 1$). Owing to the reversible nature of the photoswitching process, the catalyst can be toggled between its active and inactive forms.

In order to create such photoswitchable catalysts, photochromic moieties [1–4] have to be incorporated into the catalyst system [5, 6]. These photochromic elements can be implemented either by direct incorporation of the photochrome into the catalyst's framework or by intermolecular interaction of a suitable photochromic additive with the catalyst's active site (Figure 2). The first example of a photoswitchable inhibitor (Figure 2a) was described by Ueno and coworkers in 1980 [7]. In this pioneering study, β -cyclodextrin (β -CD), known to aid the hydrolysis of phenolic ester derivatives by providing a host for the hydrophobic aryl residue, was rendered photoswitchable by the use of 4-carboxyazobenzene as a photochromic inhibitor. The β -CD host is only able to bind the extended E-isomer of the inhibitor, whereas the kinked Z-isomer does not fit into its cavity, and hence, E \rightarrow Z photoisomerization leads to activation of the catalysts because of inhibitor displacement by the substrate. The authors further improved their system by covalently linking the azobenzene inhibitor to the catalytically active β -CD macrocycle [8, 9].

As opposed to this approach, Inoue and coworkers described the use of a photochromic activator (Figure 2b) [10]. Their catalyst system is based on the activation of aluminum porphyrins for the reaction of carbon dioxide and propylene oxide to yield cyclic propylene carbonate by axial coordination of pyridine to the aluminum center. Photocontrol could be achieved by the use of a photochromic

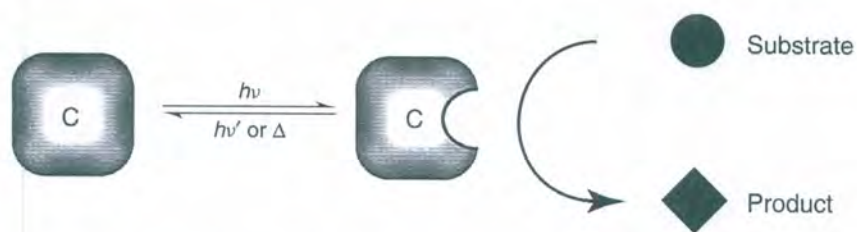


Figure 1 General concept of a photoswitchable catalyst (C).

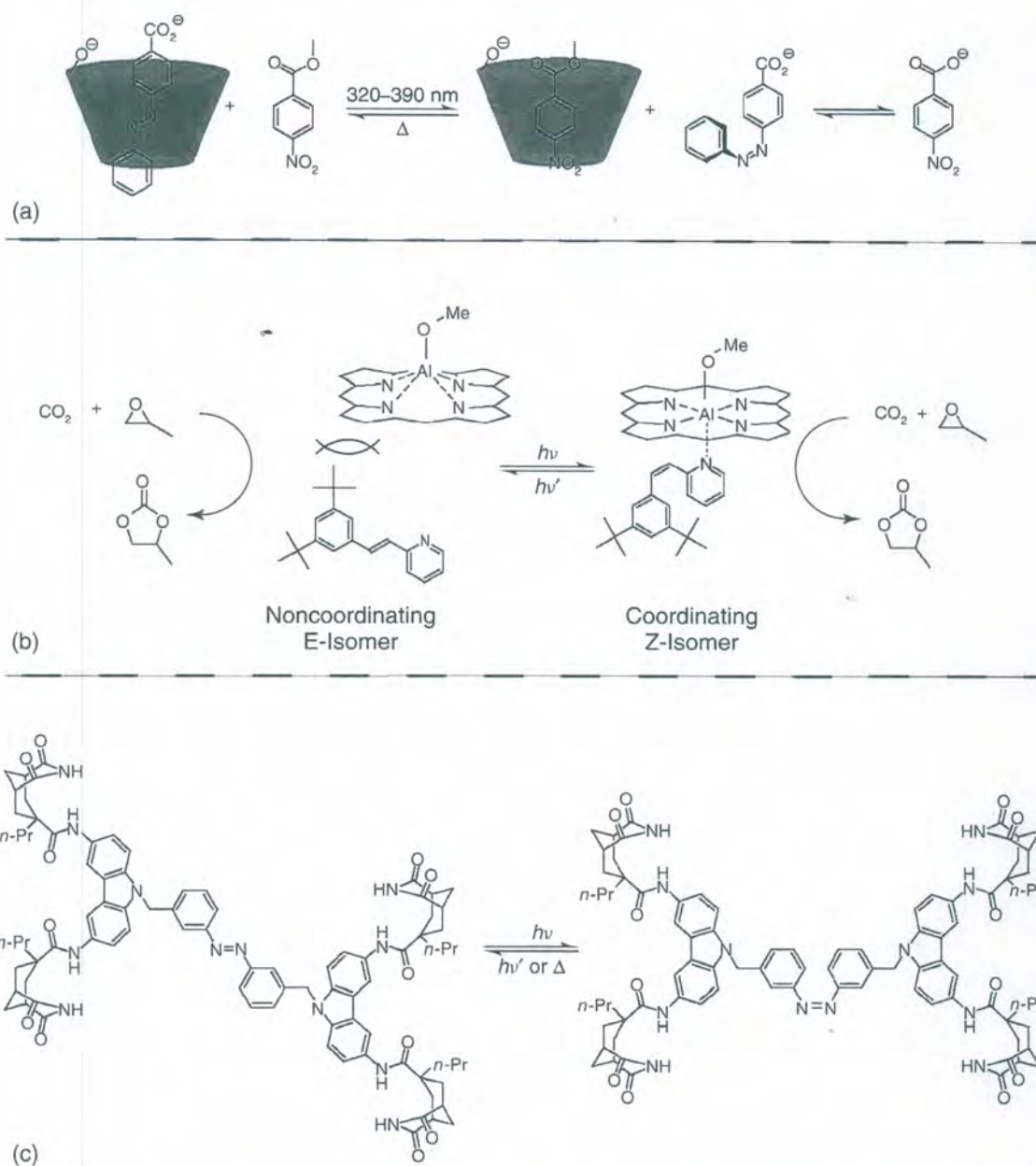


Figure 2 Key examples of photoswitchable catalysts: (a) photoswitchable inhibition of a β -CD [7], (b) activation of an aluminum porphyrin (shown as skeleton only) with a photochromic stilbazole derivative [10], and (c) utilization of an azobenzene tweezer as photochromic template [11, 12].

stilbazole derivative instead of the pyridine ligand. In the case of the E-isomer, the crowded 3,5-di-*tert*-butylphenyl moiety prevented coordination of the stilbazole moiety to the aluminum porphyrin because of steric interactions. Switching the stilbazole to the sterically less demanding Z-isomer, which is able to bind to the aluminum center, activates the catalyst system.

In a conceptually different approach, Würthner and Rebek designed a photochromic template (Figure 2c) [11, 12]. The authors connected a photochromic azobenzene core to carbazole-based receptors that efficiently bind adenine moieties. These adenine moieties were equipped with either amino or 4-nitrophenylester groups, yielding two types of guest substrates, that is, the nucleophile or electrophile, respectively. When these two guest substrates are bound to the tweezer-like Z-isomer of the template, their reactive groups are in close proximity giving rise to a significant rate acceleration of amide bond formation when compared to the use of the more extended (*E*)-azobenzene.

While these examples illustrate the potential of using photochromic moieties to control the action of a given catalyst, they suffer from various limitations, most notably the lack of generality and limited scope, product inhibition, and hence low catalytic turnover as well as small activity/selectivity ratios (ON/OFF ratios).

Strategy and Results

Our group has been working on overcoming these obstacles by designing more general and improved photoswitchable catalysts. For this purpose, we developed a steric shielding approach, which utilizes a photochromic linker to reversibly block the access to the active site of a catalyst with a rather broad reaction scope. On the basis of our initial experiences with photoswitchable metalloporphyrin complexes that, however, did not switch because of energy transfer from the photochrome to the catalyst [13], we focused on optically transparent organocatalysts, that is, catalysts with a higher HOMO–LUMO gap as compared to the photochrome. To realize a truly general catalyst, we chose to influence the reactivity of a tertiary amine, which is commonly used as a general base catalyst, by a steric shielding approach (Figure 3a) [14, 15].

In our initial design, a sterically demanding azobenzene moiety was connected in a rigid and orthogonal manner to a conformationally locked piperidine ring via a spirolactone junction (Figure 3b). In its *E*-configuration, the crowded azobenzene moiety is supposed to shield the trajectories, leading to the reactive lone pair of the piperidine's N atom. On irradiation, the *Z*-isomer is formed and thereby access to the reactive site is granted. The catalyst structure can be nicely optimized using the tricks of conformational design in organic chemistry. Thus, on the one hand, the desired piperidine's chair conformation can be locked by introducing suitable substituents, that is, *t*-butyl instead of methyl residues, thereby fixing the lone pair in an axial orientation. On the other hand, the efficiency of the azobenzene shield can be improved by introducing bulky groups, such as *t*-butyl or 2,6-dimethylphenyl substituents, in the 3,5-positions. The catalysts' structures were

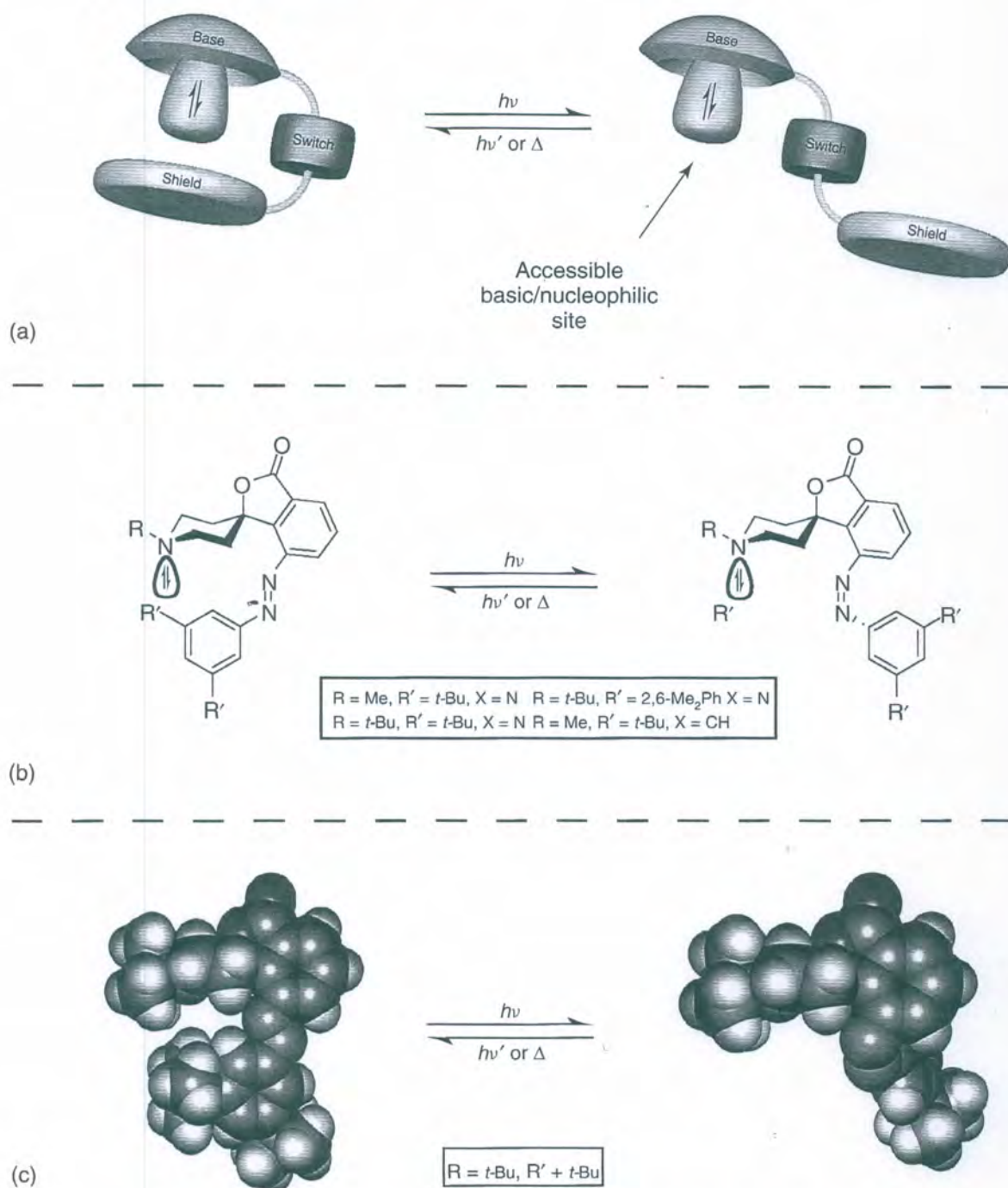


Figure 3 Photoswitchable piperidines as light-controlled general base catalysts: (a) Concept of steric shielding approach to photoswitchable bases, (b) structures of the photoswitchable piperidine bases, (c) X-ray structures of the E- and Z-isomer (van der Waals radii shown) [14, 15].

proved by single-crystal X-ray structural analysis (Figure 3c) as well as extensive NMR studies, using residual dipolar couplings [15]. Acid–base titration experiments in acetonitrile showed an enhancement of the Z-isomer’s basicity ($pK_a = 16.7$) by almost one order of magnitude as compared to the E-isomer ($pK_a = 15.9$). With respect to the small size of a proton, these changes are significant, and

more distinct effects in the interaction with bulkier electrophiles were expected. Therefore, the system was exploited as a general base catalyst in a nitroaldol addition (Henry reaction), which served as perfect model reaction because of the negligible background rate. Monitoring the formation of the adduct of nitroethane and 4-nitrobenzaldehyde by NMR allowed for the determination of rate constants for the catalysts in their ON and OFF states. By the above-mentioned fine-tuning of the catalyst structure, it was possible to increase the ON/OFF ratios from 4.3 (for $R = \text{Me}$ and $R' = t\text{Bu}$, see Figure 3b) over 13.2 (for $R = R' = t\text{Bu}$, see Figure 3b) to 35.5 (for $R = t\text{Bu}$ and $R' = 2,6\text{-Me}_2\text{Ph}$, see Figure 3b). The stilbene analog showed the lowest ON/OFF ratio and had very inefficient back switching, that is, $Z \rightarrow E$ photoisomerization. It should be noted that the azobenzene catalysts exhibit excellent switching properties, in particular high Z-content of the photostationary states as well as enhanced thermal half-lives exceeding 19 days at room temperature!

While the activity of the catalyst can be controlled by light, its selectivity relating to the formation of the *syn*- and *anti*-nitroaldol products, that is, diastereoselectivity, cannot be influenced as both products form in similar and approximately 1 : 1 ratio. Furthermore, critical analysis of our approach shows that the attainable ON/OFF ratios are limited by the choice of a catalyst with an intrinsically low reactivity. Furthermore, all catalysis experiments were performed with *ex situ* prepared E- and Z-isomers as the high optical density of the reaction mixture prevented efficient switching in solution.

One should be able to avoid this particular drawback by working on surfaces (rather than in solution). More importantly, immobilizing the catalysts on a surface allow for true harnessing of the spatial resolution possible by irradiation since catalyst diffusion is prohibited. Therefore, we synthesized an analog of the photo-switchable piperidines carrying a tether with an anchor group for covalent surface functionalization (Figure 4b) [16]. Immobilization on silica gel, serving as a model of a generic oxide surface, was achieved by reaction with a monochlorosilane functionality, which was conveniently installed via hydrosilylation of a catalyst derivative carrying a terminal vinyl group. Subsequent repeated switching cycles, monitored by UV/VIS absorption spectroscopy on colloidal suspension of silica gel particles in an isorefractive medium (CH_2Cl_2), proved complete reversibility, as it showed that the catalysts remain bound on the support. In addition, the switching induced a reversible change of the pH value of an aqueous catalyst suspension of ~ 0.3 units.

Outlook

To exploit the spatial resolution inherent in the optical stimulus, not only the catalyst but also the product have to be fixed, that is, their diffusion has to be prevented. Therefore, we are currently working on developing photoswitchable catalysts for living polymerization processes and immobilizing them on surfaces. Such systems (Figure 4a) offer great potential for surface patterning, in particular since the use of different monomers in combination with repeated light-induced activation and deactivation of defined substrate areas should allow an unprecedented complexity

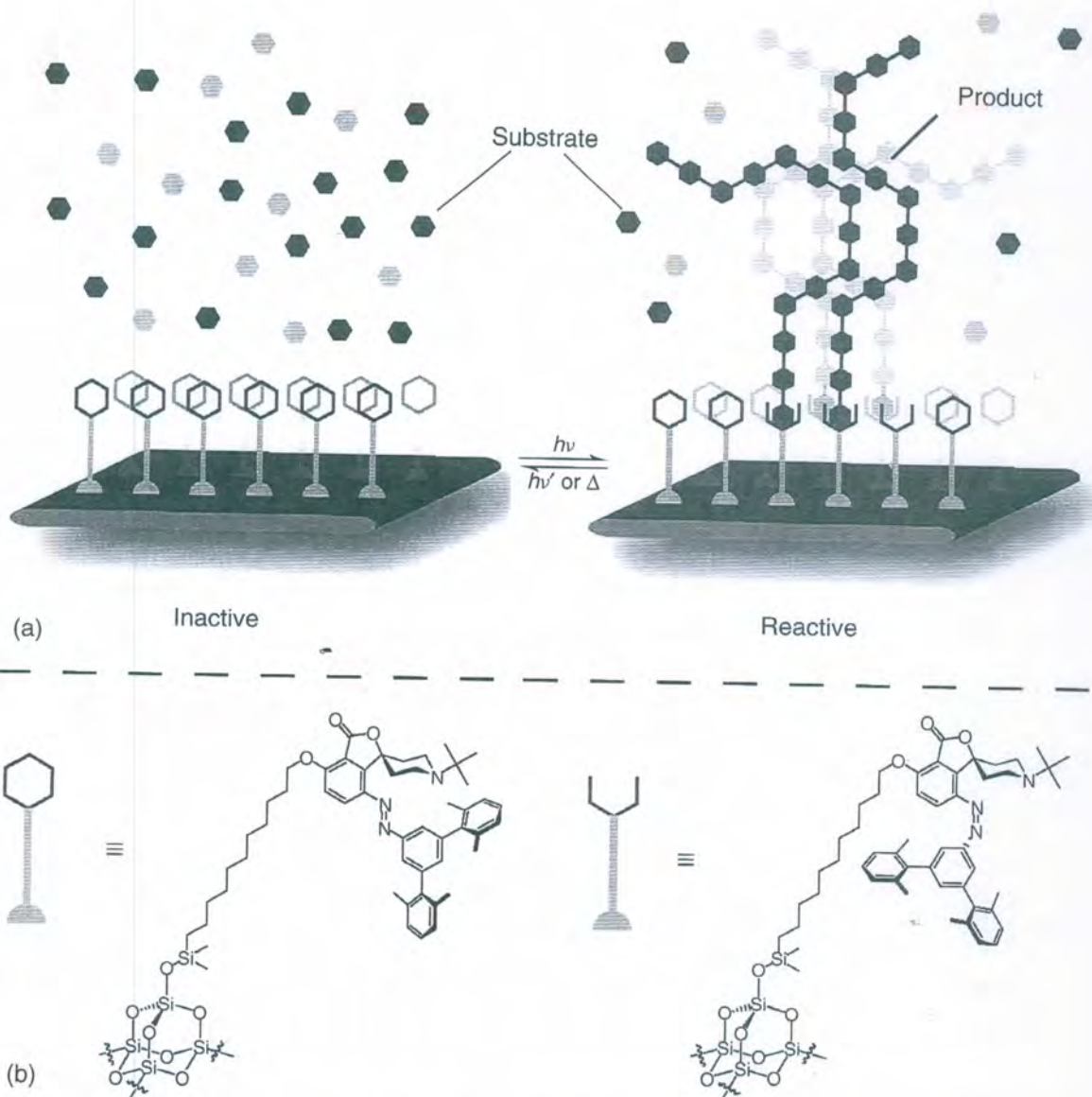


Figure 4 (a) Concept of surface patterning by immobilizing a photoswitchable catalyst for living polymerization reactions. (b) Structure of photoswitchable piperidine base immobilized on silica gel [16].

of surface structures to be realized. From a more general standpoint, it will be necessary to achieve photocontrol over more active catalytic systems, such as transition metal catalysts and powerful organocatalysts, thereby generating large ON/OFF ratios as an important prerequisite for future applications of these systems. Furthermore, not only activity but also selectivity is an attractive function to control in a catalyst system, as illustrated by an initial report by the Feringa group [17].

CV of Philipp Viehmann

Philipp Viehmann (1984) was born in Hanau (Germany) and studied chemistry at the Technische Universität Darmstadt (2004–2009) to obtain his Diploma with

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CV of Stefan Hecht

Stefan Hecht (1974) carried out his undergraduate studies in chemistry at the Humboldt-Universität zu Berlin (Germany) and obtained his Ph.D. from the University of California, Berkeley, in 2001, working under the guidance of Professor Jean M. J. Fréchet. After establishing his own research group at the Freie Universität Berlin (2001–2004) with the aid of a Sofja Kovalevskaja Award of the Alexander von Humboldt Foundation, he has been a group leader at the Max Planck Institut für Kohlenforschung in Mülheim an der Ruhr (2005–2006). Since 2006, he holds the Chair of Organic Chemistry and Functional Materials in the Department of Chemistry at Humboldt-Universität zu Berlin. His research interests range from synthetic macromolecular and supramolecular chemistry to surface science. More information can be found at www.hechtlab.de.

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