Heat and Light Switch a Chiral Catalyst and Its Products
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REFERENCES
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CRY-dependent light detection. There are ~150 neurons in the fly brain that express large amounts of the proteins involved in the circadian clock mechanism. Collectively, these 150 neurons act as a pacemaker network to control daily rhythmic behavior (5). Within that network, the eight lLNv pacemakers appear to have dedicated roles as light detectors to modulate arousal states (6–8); their levels of activation predict the fly’s subsequent levels of behavioral activity. Fogle et al. show that light controls the rate of action potential generation (the “firing” rate) of the lLNvs and then argue that this is a cell-autonomous (i.e., cell-intrinsic) response by lLNvs to light. Their most compelling experiments show that CRY expression is not only necessary but also sufficient: Misexpression of CRY by nonresponsive neurons also causes them to respond to light. This CRY-mediated electrophysiological light response in lLNvs is TIM-independent: Similar changes were observed even in flies carrying a timeless mutant. This suggests that within circadian pacemaker neurons, CRY has two distinct means of signaling light information (see the figure). This possibility was strengthened by experiments that compared the minimum light levels needed for each action. Clock resetting by CRY occurs at vanishingly low light levels (9). In contrast, increases in pacemaker firing rate required ~5 times the intensity necessary to induce CRY-TIM interaction. These higher levels correspond to natural light levels that are typically observed in early to midmorning.

These results are also striking because they reinforce several observations suggesting that the CRY family is remarkably multifunctional and diverse. As first shown in plants, CRY not only is a photosensor, but also is sensitive to magnetic fields (a magnetosensor) (10, 11). In mammals, the paralogous CRY1 and CRY2 proteins are also critical circadian elements, but not as photosensors. Instead, they form dimers with PERIOD proteins and can act as transcriptional repressors. Furthermore, in the retina, CRY mediates (directly or indirectly) the pupillary light response (12). Even among insects, the roles of CRY proteins vary. For example, butterflies have two separate cry genes: Butterfly CRY1 is a photosensor with no transcriptional activity, and butterfly CRY2 exhibits the functionality of the mammalian CRYs [i.e., with little or no photosensitivity (13)]. Fogle et al. show clearly that among insect CRYs, it is the photosensitive forms, and not the transcriptionally effective forms, that promote the direct increase in lLNv firing rate. The autonomous responsiveness of lLNvs to light is especially intriguing because it presents a striking evolutionary parallel. The response closely resembles that of intrinsically photosensitive retinal ganglion cells (ipRGCs) in mammals that express melanopsin (14). ipRGCs project to several brain regions (including the suprachiasmatic nucleus and the olivary pretectal nucleus) involved in circadian clock entrainment and radiance detection. Like the ipRGCs, lLNVs respond to light with increased action potential firing rates and, not as seen in other photosensitive sensory cells, with graded responses. Recent information indicates that ipRGCs indeed contribute to image-forming (15). The degree to which lLNVs may also contribute remains to be tested.

Xiang et al. (16) recently reported that Drosophila larvae are able to detect light via intrinsically light-sensitive peripheral neurons that tile the body wall. Apparently, these peripheral neurons (which help to drive light-avoidance behavior at high light intensities) and adult pacemaker neurons are similar, in that light responses act through novel transduction pathways in both cases. The field must now address the questions of why so much photosensitivity is distributed so broadly, across the brain and throughout the body, and whether this capacity also extends to larger-bodied animals.

References
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CHEMISTRY

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Takashi Ooi

A rotary molecular motor acts as a chiral catalyst and can produce products of either handedness after external stimuli change its structure.

A right-handed glove won’t fit a left hand because our hands are chiral. They are mirror images of each other, but despite this symmetry, their shapes cannot be superimposed one on the other. Molecules that are nonidentical mirror images are called enantiomers. Most biomolecules are found only as one of the two enantiomeric forms, and drug molecules that interact with biomolecular targets are usually more active in pure enantiomeric form. Chiral molecules can be prepared from the readily available, achiral starting materials, and many reactions that favor one chiral product (asymmetric reactions) do so by using a catalyst that itself is chiral (1). However, a versatile method must be able to make both left- and right-handed products, which usually requires having to make both enantiomers of the catalyst. On page 1429 of this issue, Wang and Feringa (2) introduce a conceptually new approach in which the structure of a single catalyst can be manipulated by cycles of light and heat to pulses. These processes drive internal rotation around a carbon-carbon double bond and create two forms of the catalysts that give reaction products of opposite chirality (3).

Many of the catalysts used for asymmetric synthesis consist of a transition metal and a chiral molecule, called a ligand, that binds tightly to the metal center (4). The choice of metal and the structure of the ligand are both critical. The use of the two different metals in combination with the same enantiomer of a ligand sometimes allows for the selective production of either product enantiomer in certain reactions (5). Chiral organocatalysts,
which are enantiopure, chiral small organic molecules, have recently emerged as a powerful alternative approach (6). Nagasawa and co-workers reported the synthesis of either enantiomer of a chiral product by changing the solvent and reaction temperature of a flexible organic catalyst (7).

However, it is very difficult to switch the handedness of the product produced by a single-enantiomer catalyst once it is in solution (8). Wang and Feringa pursued a completely different strategy. They prepared an enantiopure chiral alkene (1) (see the figure) with similar structural components on opposite sides of a double bond (the trans geometry; cis denotes the groups being on the same side). The two phenyl-substituted indane groups closest to the double bond are chiral, so they also create a helical orientation about the double bond (P and M denote right- and left-handed helicities, respectively). In addition, two functional groups often used in organocatalysis, thiourea (9) and dimethylaminopyridine (DMAP) (10), are attached to the terminal of each phenyl-indane component (orange and blue panels in the figure) (11).

Like other spatially crowded chiral alkenes, molecule 1 is a molecular motor that converts the energy provided by light and heat into repetitive one-way rotation around the central double bond. Starting from the most stable (P,P)-trans-1 configuration, the upper moiety of the molecule does one full clockwise rotation in four individual steps. Two are light-induced cis-trans isomerization associated with 180° rotation around the double bond, and the other two are inversion of the helicity controlled by heat (switching P to M). Because the terminal acidic (thiourea) and basic (DMAP) functionalities can only be in close proximity when cis isomers are generated during the rotation, Wang and Feringa envisioned that this rotary molecular motor could control asymmetric organocatalysis.

Wang and Feringa apply their system to the carbon-sulfur bond-forming reaction between thiophenol (red in the figure) and cyclohexenone (blue in the figure) (12). Cooperative effects of the two catalytic functionalities on the molecular motor can activate both reactants for bond formation. Attempts using each pre-prepared stereoisomer of 1 as a catalyst showed that only (P,P)-cis-1 and (M,M)-cis-1 exhibited sufficient catalytic performance, whereas (P,P)-trans-1 barely promoted the reaction. A different enantiomer was produced in excess (75% of one enantiomer and 25% of the other) in these two catalyzed reactions. The small amount of product obtained with (P,P)-trans-1 was a mixture of an equal amount of enantiomers.

Control of the stereochimistry of the product was also demonstrated by monitoring the dynamic behavior of the inactive (P,P)-trans-1 catalyst in a solution containing the two reactants. Ultraviolet irradiation caused rapid photochemical isomerization to the active (M,M)-cis-1, whereupon the reaction started to proceed smoothly. Additional computational analysis of the actual bond-forming stage of the reaction provides a convincing rationale for the formation of different enantiomers depending on the helicity of the cis isomers.

The work of Wang and Feringa offers unprecedented possibilities for the design of cooperative asymmetric catalysis. An important goal would be the construction of dynamic systems from a single molecular framework that can sequentially adopt defined numbers of stereoisomers in response to light or heat. Such catalysts could perform consecutive steps in the synthesis of chiral organic molecules in a single pot. Efforts in this direction may lead to the development of broadly useful catalytic machines driven by readily available physical stimuli.

Turning out different products. Two components of the rotary molecular motor [see upper left, (M,M)-trans-1] of Wang and Feringa are represented by blue and orange panels. The active functional groups are thiourea (blue circle) in one component and dimethylaminopyridine (red circle) in the other. These groups can activate cyclohexenone (blue hexagon) and thiophenol (red hexagon), respectively, as shown in the center. With the most stable (P,P)-trans-1 (upper right) as a catalyst, the active functional groups (blue and red circles) are far apart, and only a small amount of racemic product forms. Upon irradiation, the orange panel rotates to afford (M,M)-cis-1, which allows the active functional groups to interact cooperatively. This form is not only much more reactive but also creates an excess of the S enantiomer. Further isomerization to (P,P)-cis-1 by heat changes the helicity of the catalyst so that the R enantiomer is obtained with similar efficiency. This stereoisomer can be converted back to (P,P)-trans-1 by light and heat through the unstable (M,M)-trans-1.

References