**Photocatalytic deracemization fixes the mix**

Photocatalysis converts racemic mixtures of N-aryl cyclic ureas into single enantiomers

By Alison E. Wendlandt

Very often, only one enantiomer of a chiral drug molecule is clinically active; the other optical isomer can produce unwanted or even catastrophic side effects. Thus, the efficient synthesis of single enantiomers is important in small-molecule drug synthesis, and resolution methods are frequently used to enrich a molecule’s enantiomeric excess (ee) when racemic or scalemic mixtures (equal or unequal enantiomer mixtures, respectively) are obtained (1, 2). Classical and kinetic resolutions of mixtures can only reach a maximum 50% theoretical yield, and although dynamic kinetic resolution can achieve complete conversion to a single enantiomer, the resulting product is chemically modified (see the figure, top). Direct deracemization of chiral compounds reflects an ideal if rarely achieved approach to producing high-ee mixtures by resolution. On page 364 of this issue, Shin et al. (3) disclose a multicatalytic strategy for enriching racemic mixtures directly to a single enantiomer in a single step.

Deracemization methods are constrained by the principle of detailed balance, which dictates that any reverse chemical step must be in all ways microscopically identical to its corresponding forward step (4). Because (R) and (S) enantiomers are energetically identical, any elementary step or equilibrium process (catalyzed or not) that converts (R) into (S) must necessarily also convert (S) back into (R); the process will yield a racemate. Deracemization can be achieved, however, when forward and reverse steps are designed to proceed by distinct mechanisms through a common prochiral intermediate (see the figure, bottom). Highly selective precedents are limited, although several notable approaches have relied on compartmentalization to separate incompatible oxidant and reductant combinations (5, 6) or have used nonquenching redox pairs (7) to affect the desired deracemization in a single pot.

As Onsager noted in his seminal monograph (8), photochemical processes are among the handful of exceptions to the principle of detailed balance, in that forward and reverse steps may proceed along distinct electronic surfaces. A prominent example is the contra-thermodynamic photochemical isomerization of alkenes, wherein the selective absorption of light can lead to enrichment of the less thermodynamically stable constitutional isomer. This process constitutes the molecular basis for vision in vertebrates, and sensitized energy transfer has become a powerful synthetic strategy for obtaining (Z)-alkenes from (E)-alkenes through a triplet excited state (9). Extraordinary recent work by Bach and co-workers elegantly demonstrated this strategy for the catalytic deracemization of chiral allenes (10).

The method reported by Shin et al. takes a complementary photochemical approach to catalytic deracemization. Instead of energy transfer, the authors use an iridium photocatalyst to promote reversible electron transfer (ET) from the substrate. Enantioselective deprotonation (proton transfer, PT) of the resulting radical cation occurs in the presence of a chiral phosphate base to form a prochiral neutral radical intermediate with a net loss of a hydrogen atom from the substrate. This step functions as a photoinduced kinetic resolution, selectively ablating the stereochemical information of the faster-reacting (S)-substrate and enriching the once-racemic starting mixture in the (R)-substrate. The radical intermediate then reacts with a chiral thiol in an enantioselective hydrogen-atom exchange.
transfer (HAT) step, this time kinetically favoring the formation of the (R)-substrate. Substoichiometric quantities of both the chiral base and chiral thiol can be used. The overall process consumes only photons, unlike thermal redox deracemizations, where stoichiometric oxidants and reductants are necessary to drive the reaction toward a single enantiomer.

The net result is a highly selective synthetic deracemization of N-aryl cyclic urea substrates. Yet remarkably, neither of the two individual steps (ET-PT and HAT) proceeds with high selectivity. Mathematically, the selectivity-determining step (SDS) is a composite of the two individual steps, and the observed enantiomeric ratio is the sum of the enantiomeric ratios of the two individual steps. The multiplicative form of the SDS results in extremely high overall enantio-meric enrichment through the synergistic action of these two chiral catalysts, even though each catalyst working individually is not particularly selective.

Although the scope of the reaction reported by Shin et al. is restricted to proof-of-concept substrates, undoubtedly exceptional cases such as this will become more common. In particular, the structural similarity of the current substrates to important classes of chiral ligands (for example, oxazolidinones) and to intermediates in enzymatic deracemization and stereoconversion pathways (for example, hydantoinase-decarbamoylase systems) hints toward the possibility of expanding this approach to the deracemization of amino acids and other important chiral molecules.

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PHOTOSYNTHESIS

Photosystem II, poised for O₂ formation

By R. David Britt and David A. Marchiori

The vast majority of oxygen in Earth's atmosphere is generated by photosynthetic light reactions. This process also plays an integral role in producing energy for Earth's biosphere. Photosystem II (PSII) uses visible light to oxidize water and release O₂. Its oxygen-evolving complex (OEC) sequentially advances from its most reduced state (S₀), through four photon-driven oxidations, to its most oxidized state (S₄), which produces O₂. As described on page 334 of this issue, Suga et al. used a powerful x-ray free-electron laser (XFEL) to examine in structural detail the OEC just prior to O=O bond formation, thereby adding to a growing body of work in this area. Such mechanistic details of the OEC’s operations could help in the development of synthetic solar fuel reactions aimed at sustainable fuel production from water and sunlight.

The chemistry of the PSII water oxidation process has been the focus of studies coupling molecular biology and biochemistry to spectroscopic methods (2, 3). For many years, progress in the field was made without a structural basis for interpretation, but since the early 2000s the field has greatly benefited from steadily improved x-ray crystal structures of PSII nominally poised in the dark stable state (Sₐ) (4–6).

The Sₐ-state OEC is a Mn₅CaO₂ cluster, and the structural changes that occur in this cluster as it advances through the light-driven S-state transitions are a major question in the field. Coupled to these structural changes are questions concerning the S-state transitions in which the two substrate waters bind to the cluster and in what chemical form (e.g., H₂O, OH⁻, bridging, or terminal O²⁻). This is additionally complicated by the presence of an abundance of oxo bridges (a water-derived oxygen molecule that bridges two or more Mn/Ca ions) and water molecules within and proximal to the OEC. Which of these are the actual substrates that are oxidized to form O₂?

In one scenario, both substrate waters could bind to the OEC following O₂ release in the Sₐ-to-S₄ transition. In this case they should be present as OEC ligands in the dark stable Sₐ structure, where two waters (W1 and W2) are bound to a “dangler” Mn⁴ (7) and another two waters (W3 and W4) are bound to the Ca ion. This geometry suggests one often-discussed model for O=O bond formation, in which the dangler Mn⁴ (or another Mn of the cluster’s core) is oxidized to a highly electrophilic Mn(V)-oxo species by the S₄ state. The Mn(V)-oxo could then be attacked by a nucleophilic water or hydroxide on the adjacent Ca ion (2, 5).

However, it is also plausible that one or both waters bind to the OEC later in the S-state cycle, arriving from nearby solvent water site(s). Siegbahn’s proposed model, based on density functional theory (DFT) energetics calculations, suggests that a water binds to an open coordination site at Mn¹ in the Sₐ-to-S₄ transition (8), which upon further oxidation to S₄ forms a Mn⁴(IV)O₂ species that creates the O=O bond through a radical coupling to the bridging O5 (see the figure). The conversion of a five-coordinate Mn⁴(IV) to a six-coordinate Mn⁴(IV) at the S₄ state, with a new water binding to Mn¹ at S₄, has been supported by recent high-field electron paramagnetic resonance (EPR) spectroscopy studies (9, 10).

XFELs produce pulses of a few femtoseconds’ duration with high enough photon energy and flux for use in electron diffraction of microscale protein crystals. This tool has been used to study the OEC’s water oxidation mechanism. XFEL pulses are sufficiently short that the desired x-ray diffraction occurs before the microscale crystals are destroyed. The XFEL pulses can be synchronized with visible-light laser pulses to drive the S-state advancement. PSII is a particularly good target for this approach because short visible-light pulses drive the water-splitting reaction. This has allowed investigators to probe the structures of the transient Sₐ and S₄ states, with several recent studies focused on the latter state, which is only 1 flash/electron transfer from the formation of O₂ (11–13).

There are many important aspects to these advanced S-state structures, but the question of substrate binding at the S₄ state is particularly crucial, as this is key to proposed...
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Science 366 (6463), 304-305.
DOI: 10.1126/science.aay6919

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