ENZYME MIMICS

Halogen and chalcogen team up

The behaviour of di-selenol enzyme mimics indicates that a halogen bond between selenium and iodine, and a chalcogen interaction between the two selenium atoms, play an important role in the activation of thyroid hormones.

Pierangelo Metrangolo and Giuseppe Resnati

Iodine and selenium are essential trace elements of fundamental importance to human health. The thyroid gland, for example, uses iodine to make thyroid hormones — which are important for the function of every cell in the body owing to their role in regulating cell growth and differentiation, and in increasing the metabolism of proteins, lipids and carbohydrates. In turn, their activity is controlled by a family of seleno-enzymes, the iodothyronine deiodinases (IDs).

The ID enzymes activate and inactivate the thyroid hormones by cleaving iodine atoms at specific positions. The pro-hormone thyroxine T4 (3,5,3′,5′-tetraiodothyronine, Fig. 1) is the storage form of the hormone in the blood. To become biologically active, it needs to be converted to its T3 form (3,5,3′-triiodothyronine) by removal of the iodine in the 5′ position on the outer ring; this step is carried out by the type-1 and -2 deiodinases (ID-1 and ID-2). Deiodination carried out by the type-3 enzymes (ID-3), however, occurs at a different position — the 5 site on the inner ring — and instead converts T4 into an inactive isomeric form, rT3 (3,3′,5′-triiodothyronine). All three ID enzymes also slowly catalyse further deiodinations of T3 and rT3 to a series of di- and mono-iodo derivatives.

All three enzymes contain at their active site a selenocysteine residue — often referred to as the twenty-first amino acid — that is known to be important for their biological activities[1], yet its specific role has remained largely unknown. Nevertheless, several studies with native proteins and their mutants have revealed unexpected complexities in the deiodination reaction mechanism. Some insight has also been gained through studying a set of small-molecule mimics of IDs. Theoretical investigations have also suggested that halogen bonds[2] may play an important role in T4 deiodination[3]. The ability of T4 to be involved in this type of interaction was confirmed by, among other factors, the short I···O contacts formed on bonding to transthyretin, its serum carrier[4]. Further mechanistic investigations on the outer-ring 5′-deiodination of T4 have also been performed with synthetic selenols (Ar-SeH), and this led to the suggestion that it involves a nucleophilic attack of the selenol on the iodine atom[5].

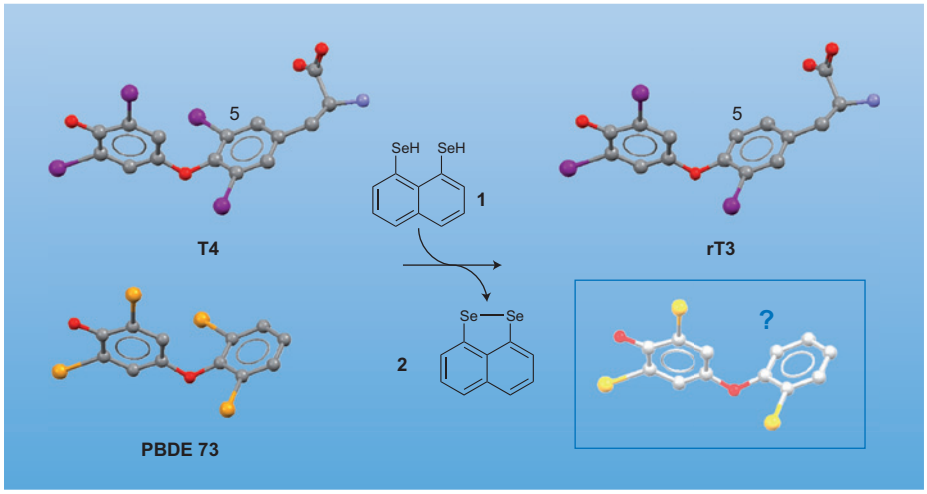

Figure 1 | The *peri*-substituted naphthalene-diselenol **1** efficiently removes iodine (shown in purple) from the inner ring of thyroxine (3,5,3′,5′-tetraiodothyronine, T4), yielding 3,3′,5′-triiodothyronine (rT3) (top). Mechanistic investigations reveal that the formation of a halogen bond between the iodine and selenium atoms and a concomitant selenium–selenium bond formation between the two *peri*-positioned chalcogen atoms, yielding **2**, are needed for the deiodination reaction to occur. This finding could be important for the remediation of polyhalogenated organic pollutants, such as PBDE 73 (bottom, left), if a similar mechanism is found to be able to activate the C–Br bond cleavage.

As they describe in the *Journal of the American Chemical Society*, Debasish Manna and Govindasamy Mugesh[6] have now unambiguously demonstrated that the iodine atoms of T4 feature regions that are significantly positively charged (σ-holes) and thus provide possible sites for halogen bonds with selenium.

A variety of simple selenol species were chosen as enzyme mimics. When a monoselenol compound such as benzene- or 1-naphthalene-selenol was treated with T4 under physiologically relevant conditions, no deiodination on the inner ring was observed, indicating that a 'standard' I···Se halogen bond — that is, the transfer of electron density from selenium to iodine — is not strong enough to cause the activation and cleavage of the C–I bond. The same happened when the selenol compound was rendered more nucleophilic by grafting an alkyl–amino side chain on the benzene ring.

In contrast, the *peri*-substituted naphthalene-diselenol **1** successfully cleaves an iodine atom efficiently from the inner ring of T4, yielding rT3 (Fig. 1). Mechanistic investigations revealed that the concomitant formation of an iodine–selenium halogen bond and formation of a selenium–selenium bond between the two *peri*-positioned chalcogen atoms were both important for the deiodination reaction to occur.

In fact, the marginal decrease in electron density at the halogen-bonded selenium is somewhat compensated by the second selenol group, through neighbouring group participation. In turn, the rate of the C–I bond cleavage can

also be increased by further modifying the structure of the diselenol molecule. If additional nearby lone pairs — introduced by grafting alkylamino side chains — are involved in counterbalancing the electron-density depletion at the halogen-bonded selenium, the anchimeric assistance to C–I bond cleavage becomes even more effective. This is the case, for example, when 7-amino-methyl-1,8-naphthalene-diselenol is used. The stronger the interaction between the *peri*-positioned chalcogen atoms, the stronger the I···Se halogen bond and the faster the deiodination rate.

The key finding of Manna and Mugesh is that although the formation of any I···Se halogen bond elongates — and thus weakens — the C–I bond, an effective bond activation resulting in bond cleavage begins to occur only when two chalcogen atoms are in the *peri* position. This means that they interact with each other in a way that facilitates the transfer of a higher electron density to the C–I σ^* orbitals through halogen bonds. Substitution by sulfur of either one or both selenium atoms of the *peri*-naphthalene-diselenol (**1**) considerably decreases the effectiveness of the deiodination. As a selenol is more nucleophilic than a thiol, the proposed rationalization may also provide a convincing explanation for nature's preference for selenium at the active site of deiodinases.

When a deiodination reaction is mediated by the enzymes ID1 and ID3, only one selenium centre is present, the catalytically active selenocysteine — but a thiol group present on the neighbouring cysteine residue may interact with the selenium atom of the selenocysteine to promote the C–I bond cleavage.

By experimentally demonstrating that halogen bonds may play a key role in enzyme-catalysed deiodination, the study by Manna and Mugesh may add a new biologically important function to those already known for the interaction[7]. More importantly, their findings open new perspectives in the activation of carbon–halogen bonds — a vital issue in the bioremediation of polyhalogenated organic pollutants, such as polybrominated diphenyl ethers (PBDEs). PBDEs are a class of flame retardants that have been highly accumulated in sediments, and PBDEs hydroxylated in the *para* position and possessing two bromine substitutions adjacent to the hydroxyl group are known to show a remarkable thyroid hormonal activity[8]. This is not surprising considering the structural similarity of thyroxin and PBDEs (Fig. 1, bottom left), which strongly suggests a similar receptor activity. Taking inspiration from nature, the reagents reported by Manna and Mugesh may help the design of innovative biomimetic systems for the bioremediation of polyhalogenated organic pollutants. ❐

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ASYMMETRIC CATALYSIS

The power of pairing

Supramolecular catalysts that combine an anionic chiral scaffold, a cationic coordinating structure and a metal centre have been shown to be highly effective for asymmetric synthesis. The success opens a new avenue for the design of new catalysts with a wide variety of chiral environments.

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One of the keys to the success in the development of transition-metal-mediated asymmetric catalysis is the design and synthesis of chiral ligands. Two structural features are essential in any chiral ligand: a chiral scaffold and metal coordinating site(s). Consider, for example, the highly successful BINAP ligand (Fig. 1a), a bidentate phosphine widely used in asymmetric catalysis, which is perhaps most famous for its application as a ligand for rhodium in the asymmetric hydrogenations that earned Noyori and Knowles a share of the 2001 Nobel Prize for Chemistry. The chirality of the ligand results from restricted rotation around the hindered biaryl bond, and the two phosphorus atoms provide the metal coordinating sites.

Although enormous research efforts have been invested in the synthesis of such compounds, the development of new chiral ligands remains a challenge. Multiple synthetic steps are often required, and phosphines in particular can be problematic as they can be easily oxidized.

Identifying the best ligand for any particular catalytic asymmetric reaction can be difficult. A huge variety of ligands are now known that combine many different coordinating atoms, coordination modes and chiral scaffolds. Moreover, the yields and selectivities observed in catalytic asymmetric reactions are often highly dependent on substrate. So although some families of ligands have been successfully applied in many different reactions, it can be difficult to predict a priori which ligand will be most successful for any particular case, making extensive ligand optimization a necessity.

Nature, meanwhile, can take a relatively small number of building blocks and produce enzymes that catalyse asymmetric reactions with exquisite selectivity. Taking inspiration from this, several researchers[1–4] have turned to a supramolecular approach to the construction of chiral ligands. Where conventional chiral ligands rely on the formation of covalent bonds, the supramolecular approach relies on spontaneous self-assembly of the most thermodynamically stable structure after mixing several small components. The synthesis of each small component is in principle much easier than the synthesis of the more complex chiral