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Complementary oxidation of agrochemicals and intermediates by class I and II unspecific peroxygenases

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Selective oxidation reactions can be a useful tool in the generation of metabolites of bioactive compounds for analytical and toxicology studies. In this study, we show that a range of commonly encountered agrochemicals and synthetic intermediates can be selectively oxidised to form valuable precursors and metabolite compounds using the complementary activities of class I and class II unspecific peroxygenases (UPOs) on preparative scale, permitting full product characterisation. In this way, several UPO-mediated biotransformations of agrochemically relevant intermediates have been uncovered; these include the hydroxylation of phenylureas and isoxazolidinones and the N-dealkylation of triazines. Hence, the herbicide clomazone was hydroxylated by the class I artUPO to give 5-hydroxyclomazone in 27% isolated yield, but was not transformed by the class II UPO rAaeUPO-PaDa-I-H. However, the class II UPO could be used to transform isoproturon to give the hydroxylated product 2-hydroxy-IPU with 57% isolated yield.

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Since their discovery in 2004 by Hofrichter and coworkers, 1,2 unspecific peroxygenases (UPOs)3-5 have emerged as useful biocatalysts for the selective oxygenation of small organic compounds. UPOs, which are secreted fungal enzymes, display advantages over competing hydroxylation biocatalysts, in that, unlike the well-studied cytochromes P450,6-8 UPOs can be produced and applied at scale in vitro and depend only upon the addition of hydrogen peroxide (H2O2) as an external oxidant, eliminating the need for nicotinamide cofactors or electron transfer proteins. In recent years, genome mining and bioinformatics studies have revealed many different UPOs in fungal organisms, 9,10 and these have been broadly divided into two classes, based on their molecular weight. Hence, class I UPOs are typically of the order of 26 kDa, and include enzymes such as MroUPO from Marasmius rotula, 11 DcaUPO from Daldinia caldariorum¹² and HspUPO from Hypoxylon sp. EC38. 13 Class II UPOs are typically larger, at around 45 kDa, and include the prototypical enzyme AaeUPO from Agrocybe aegerita,2 but also PabUPO from Psathyrella aberdarensis14 and GmaUPO from Galerina marginata.15

Our recent studies have focused on one from each class of UPOs: 'artUPO' is named for 'artificial peroxygenase' and is a variant based on the sequence of the class I UPO from Marasmius rotula described in a patent in 2016. 16 In common with MroUPO, 17 it can be expressed in E. coli, 18 but we have previously determined that the enzyme, when expressed in Pichia pastoris, performs better in oxidation reactions owing to superior stability to process conditions. 18 artUPO and its mutants have been shown to catalyse a number of interesting transformations, including hydroxylation, 18 S-oxidation 18 and also cyclopropanation. 19 rAaeUPO-PaDa-I-H is a variant of the class II UPO mutant from Agrocybe aegerita that was initially developed by Alcalde and co-workers, 20,21 and has also been shown to catalyse a number of interesting reactions by their group and other groups.^{5,22-24} In addition, we have shown that the enzyme is capable of promiscuous catalysis of reactions such as the Achmatowicz reaction²⁵ and also aromatic halogenation reactions.26

In addition to molecular weight, the two classes of UPOs feature different access tunnel and active site topologies that exert different constraints upon their substrate spectra. 18,27-29 While both active sites are generally hydrophobic, class I UPOs typically feature fewer bulky phenylalanine residues than class II UPOs, and consequently are able to bind and oxygenate larger substrates. Class II UPOs, however, have advantages in that their sterically hindered active sites bind and transform smaller substrates more selectively. For example, the class I UPO artUPO transforms the unsaturated

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terpene 3-carene by epoxidation, whereas the class II rAaeUPO-PaDa-I-H oxygenates the exocyclic methyl group of the same substrate.³⁰ In addition, simple thioether substrates such as *para*-tolyl methyl sulfide are converted into (*R*)-sulfoxides by rAaeUPO-PaDa-I, with very high ee, but to the (*S*)-enantiomers, with reduced ee, by artUPO.¹⁸ These differences provide a natural toolbox for diverse oxygenation catalysts and platforms for evolution studies that look to expand the substrate range of natural enzymes.

The diverse reactivity exhibited by UPOs has been exploited in the transformation of several interesting substrate types, evidencing the role of UPOs as valuable generalist enzymes in substrate oxygenation. For example, Hofrichter and co-workers established that significant environmental pollutants, including chlorobenzenes 1 and polycyclic aromatic hydrocarbons (PACs) such as acenaphthylene 3, are transformed into hydroxylated products by UPOs (Scheme 1a).³¹ In addition, Hofrichter³² and also Hollmann and co-workers³³ have demonstrated the utility of UPOs for the production of metabolites of commonly prescribed pharmaceuticals, including tolbutamide 5 and naproxen 7 (Scheme 1b).

As part of a collaboration with our industrial partner, Syngenta, 34 we were interested to explore if UPOs could also be applied to the generation of intermediates and metabolites that were of relevance to another large sector in fine chemicals manufacture, that of agrochemicals (Scheme 1c). Although structurally diverse, many of these compounds, such as the phenylurea class herbicide isoproturon 9, contain multiple potential sites for modification by, for example, hydroxylation 10 or demethylation 11 that can lead to valuable agrochemical metabolites, which, in many cases, are biomarkers for human metabolism. In this report, we show that the activities of two enzymes representative of class I and class II UPOs offer complementary routes for the generation of various oxidation products, some of which are agrochemical metabolites, starting from the same substrates. Moreover, we show that the enzymes may be applied at preparative scale to generate up to 10 s of mgs of pure products suitable for analytical or toxicology studies.

Scheme 1 UPOs as broad-spectrum oxidants in compound oxygenation: a: as applied to environmental pollutants; b: as applied to pharmaceuticals; c; as applied to agrochemicals.

Screen of agrochemicals for UPO-catalyzed oxygenation

Twenty-eight agrochemicals including widely used herbicides and fungicides were selected for the screening using class I artUPO16,18 and class II rAaeUPO-PaDa-I-H20,21,35 as the biocatalysts. The two enzymes were expressed in the yeast Pichia pastoris as described previously, 18,35 and used as either lyophilised powder or crude secretates from yeast fermentation. Small-scale biotransformations (0.5 mL) were initially conducted using standard conditions in phosphate buffer pH 7.0, but instead of adding H₂O₂ to the reactions, an enzymatic peroxide generating system was applied, which used glucose oxidase (GOX) and glucose, as applied by König and co-workers.³⁶ Reaction mixtures were incubated for 18 h and the reactions were analysed by LC-MS. Of the 28 substrates tested, 12 substrates were not converted by either UPO, while 16 were converted by one or both enzymes, with the successful transformations summarised in Fig. 1. A comprehensive list of all substrates used in this small-scale screen, including LC-MS details, is given in the SI (Sections S3 and S4).

For the presentation and discussion of results, compounds have been loosely divided into structural types; simple aromatics 12–14, 27; amides, ureas and carbamates (9, 15–18, 26), N-heterocycles (19–22) and halogenated aromatics (23 to 25). The significant differences in the conversion observed for the two different UPOs, seen across all substrates 9–26, provide strong supporting evidence that the transformations are

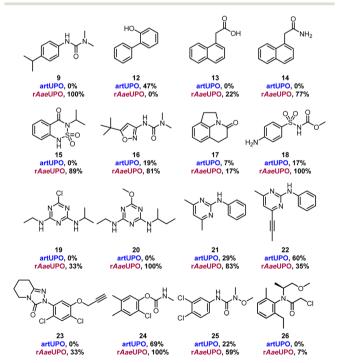


Fig. 1 Summary of substrates undergoing conversion (%) in an LC-MS screen of agrochemical oxygenation by rAaeUPO-PaDa-I-H ('rAaeUPO') and artUPO.

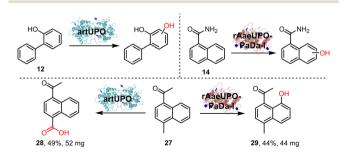
primarily mediated by the UPO, and not by other components in the *Pichia* secretate or by direct oxidation by H₂O₂.

All of these compounds were transformed by one enzyme or by both and are discussed in more detail in the following sections, including scale-ups for the most effective biotransformations. Larger structures, such as oxaziclomefone S1, prosulfuron S2, azoxystrobin S3, propiconazole S4, diflufenican S5, isoxaflutole S6, befultamid S7, methoxyfenazide S8, the chloroaromatic alkyne propyzamide S9, boscalid S10, pyriproxyfen S11, and nicotine S12, were not converted by either enzyme in the small-scale screen and are not discussed further (see SI Section S3 for the chemical structures of S1-12).

Simple aromatics

Complementary catalytic behaviour of the two enzymes was observed in simple diphenyl compounds. The fungicide 2-phenylphenol 12, for example, was hydroxylated by artUPO but not rAaeUPO-PaDa-I-H (Scheme 2). The biotransformation of 12 is also catalysed by the well-studied 2-hydroxybiphenol 3-monoxygenase (HbpA).37 However, 1-naphthyl substrate 1-naphthyl carboxamide 14 was only hydroxylated by rAaeUPO-PaDa-I-H. The regioselectivity of hydroxylation was not determined in these cases, but 47% and 77% conversions of 12 and 14 into mono-hydroxylated derivatives were observed by LC-MS.

4'-Methyl-1'-acetonaphthone 27, a synthetic precursor of isoxazoline pesticides such as afoxolaner, underwent regiocomplementary reactions, as artUPO oxidised the exocyclic methyl group into the carboxylic acid product 4-acetyl-1naphthoic acid 28. In contrast rAaeUPO-PaDa-I-H only hydroxylated on aromatic carbon 1 to give product 29, which is a similar reaction to that reported for the hydroxylation of naphthalene by a mutant AaeUPO.38 Each of the transformations of 27 was performed on a preparative scale, starting with 92 mg of 27, yielding 52 mg and 44 mg of products 28 and 29 respectively (Scheme 2). Note that for this preparative scale reaction (and most subsequent cases), a slow H₂O₂ delivery system via a syringe pump was utilised, rather than the GOX system used in the small-scale screen, as this method tends to lead to improved conversion in preparative scale UPO transformations 19,24-26,30 (see SI for full preparative details).



Scheme 2 UPO transformations of simple aromatics.

Amides, ureas and carbamates

The herbicide clomazone 30 was hydroxylated by artUPO to give 5-hydroxyclomazone 31 but it was not transformed by rAaeUPO-PaDa-I-H (Scheme 3). Full characterisation of 31 was achieved on a pure 14 mg sample derived from a preparative biotransformation on 48 mg scale. This reaction is noteworthy, as previous biotransformations of 30 by, for example, Aspergillus niger that have yielded 31 as a product, have done so only as a proportion of a mixture of other products.³⁹ Metolachlor 26 underwent demethylation based on LC-MS analysis on smallscale with rAaeUPO-PaDa-I-H, presumably at the methoxy group, but with low conversion (7%). The phenylurea class herbicide isoproturon (IPU) 9 was not transformed by artUPO, but it was transformed by rAaeUPO-PaDa-I-H to give hydroxylated product 2-hydroxy-IPU 10 and also the N-demethylated hydroxylated product 11, each of which are known microbial metabolites of 9,40 in 57% and 15% isolated yields respectively, from a 100 mg scale reaction. The hydroxylation of the isopropyl methylene resembles a similar selectivity in the transformation of menthol by rAaeUPO-PaDa-I-H.30 Bentazon 15 was not transformed by artUPO, but was converted into a complex mixture of products by rAaeUPO-PaDa-I-H. Isouron 16 appeared to be hydroxylated by artUPO (18% conversion based on LC-MS data), but the conversion was more significant (81%) with rAaeUPO-PaDa-I-H. Isouron is an isoxazolylurea herbicide that has previously been the subject of microbial metabolism studies in which the fungus Rhizoctonia solani was observed to metabolise this compound through oxidative dealkylation of nitrogen and also methyl hydroxylation at the tert-butyl group. 41 The structures of the rAaeUPO-PaDa-I-H biotransformation products were confirmed on scale up as the N-formyl metabolite 32, isolated in 35% yield, and also product 33 (arising from demethylation plus hydroxylation) in 19% yield. Both products were isolated cleanly from a 51 mg-scale preparative biotransformation and

Scheme 3 UPO transformations of amides, ureas and carbamates.

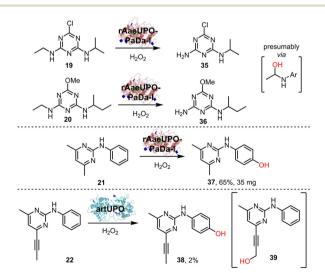
fully characterised by 1H and 13C NMR to confirm their structural assignments.

The fungicide pyroquilon 17 was hydroxylated by both rAaeUPO-PaDa-I-H and artUPO, based on LC-MS analysis, in the small-scale screen (see SI, Fig. S11), although the structure of the product was not determined. Interestingly, asulam 18 was transformed into a compound with approximately double its molecular weight, indicating dimerisation. It has recently been shown that anilines can be coupled by AaeUPO-PaDa-I through formation and spontaneous coupling of nitroso derivatives. 42 Analysis of a pure sample of the product following a preparative scale biotransformation on 115 mg scale confirmed the structure of the azoxy product 34, which was obtained in 61% isolated yield.

N-heterocycles

Atrazine 19 was de-ethylated by rAaeUPO-PaDa-I-H based on LC-MS data, to give 35 (Scheme 4). The closely related compound secbumeton 20 was also de-ethylated by the same enzyme to give product 36, with full conversion observed in this case. N-Dealkylation has previously been established as an activity of wild-type AaeUPO and AaeUPO-PaDa-I in the transformation of, for example, pharmaceuticals such as lidocaine⁴³ and also of N,N-bis(2-hydroxypropyl)-p-toluidine (NNBT), a constituent of composite epoxy resins. 44

The fungicide pyrimethanil 21 was hydroxylated to 37 by rAaeUPO-PaDa-I-H and related compound mepanipyrim 22 was also hydroxylated, but by artUPO, to give 38 (Scheme 4). The preparative-scale synthesis of 37 was achieved using rAaeUPO-PaDa-I-H and three equivalents of hydrogen peroxide on a 50 mg scale to give pure 37 (35 mg, 65% yield) (Scheme 4). The aromatic hydroxylation of polyaromatic systems by the class II UPO resonates with previous transformations of, for example, flavonoids by wild-type AaeUPO.45 4-Hydroxy-pyrimethanil 37 is the major human metabolite of 37 and has been used as a biomarker for



Scheme 4 UPO transformations of N-heterocycles.

Scheme 5 UPO transformations of halogenated aromatics

exposure to this compound. 46 Menapyrim 22 presents a more sterically challenging analog of 21 and indeed rAaeUPO-PaDa-I-H was not observed to transform the larger compound. However, artUPO, which has been shown to successfully transform larger substrates,30 was shown to give phenol product 38 via a preparative scale biotransformation, although the isolated yield (2%) was very low. The metabolism of mepanipyrim 22 has been studied previously using whole cell preparations of the fungus Cunninghamella echinulata, which gives the major metabolites 38 and 39, with hydroxylation on the terminal methyl group of the alkyne substituent as shown in Scheme 4.47

Halogenated aromatics

The herbicide azafenidin 23 was hydroxylated to give 40 by rAaeUPO-PaDa-I-H (Scheme 5) on preparative scale, albeit in very low yield. The insecticide carbanolate 24 was transformed by both rAaeUPO-PaDa-I-H and artUPO to give hydroxylated products 41 as determined by LC-MS analysis. The herbicide linuron 25 was dealkylated by rAaeUPO-PaDa-I-H to give 1-(3,4dichlorophenyl)-3-methoxyurea (DCXU) 42, mammalian metabolite of linuron.⁴⁸ The structure of 42 was confirmed by analysis of the product purified from a 149 mg scale biotransformation that gave an 18% isolated yield.

Conclusions

The selective generation of oxidised metabolites of bioactive agrochemical compounds could be important for toxicity studies that establish the effects of those metabolites on biological systems. 49,50 It could be especially useful if these syntheses can be achieved through microbial enzymatic means, as these can be used as a preferable alternative to, for example, microsomal P450 preparations. The studies presented show that UPOs present simpler microbially-derived systems for scalable metabolite generation that do not depend upon nicotinamide cofactors or electron transport proteins. They also demonstrate that within even a small subset of enzymes, sufficient diversity exists to offer options for successful transformation when some enzymes fail and also in some cases complementary specificity

for the same substrate. Hence, the major oxidative metabolic transformations: hydroxylation (and further oxidation) and demethylation, can be achieved by using complementary enzymes identified even from very limited screens. This complementarity can be achieved, for example, through the contrasting steric and electronic factors exerted by the class I artUPO and class II rAaeUPO-PaDa-I-H as demonstrated in these studies. This has permitted, for example, the successful transformation of the sterically challenging menapyrim 22 by artUPO, when no transformation could be achieved with the enzvme. The different outcomes biotransformation of 4'-methyl-1'-acetonaphthone 27 are also notable, with methyl and aromatic hydroxylation/oxidation targeted by class I and class II enzyme, respectively. Larger screens of more UPOs and their variants are very likely to identify further transformations of interesting substrates with useful complementary selectivities.

Author contributions

N. P. M., C. M., J. C., A. G., W. P. U. and G. G. designed and supervised the experiments. B. M., C. M. and K. A. S. C. performed the experiments. W. P. U. and G. G. wrote the manuscript with contributions from all authors.

Conflicts of interest

There are no conflicts to declare.

Data availability

Supplementary information: SI contains procedures for biotransformations, results of screens and analytical data for isolated products. See DOI: https://doi.org/10.1039/ D5CY00933B.

The data supporting this article have been included as part of the SI.

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