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Modeling the formation and reactions of benzene metabolites

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ABSTRACT

One or more of the muconaldehyde isomers is a putative product of benzene metabolism. As muconaldehydes are highly reactive dienals and potentially mutagenic they might be relevant to the carcinogenicity of benzene. Muconaldehydes may be derived through the action of a cytochrome P450 mono-oxygenase on benzene oxide–oxepin, which are established metabolites of benzene. Oxidation of benzene oxide–oxepin either by the one-electron oxidant cerium(IV) ammonium nitrate (CAN) or by iron(III) *tris*(1,10-phenanthroline) hexafluorophosphate in acetone at −78 °C or acetonitrile at −40 °C gave (*E*,*Z*)-muconaldehyde, which was a single diastereoisomer according to analysis by ^{1}H NMR spectroscopy. Reaction of toluene-1,2-oxide/2-methyloxepin with CAN gave (2*E*,4*Z*)-6-oxo-hepta-2,4-dienal. Similarly, the action of CAN on 1,6-dimethylbenzene oxide-2,7-dimethyloxepin gave (3*Z*,5*E*)-octa-3,5-diene-2,7-dione. *In vivo*, benzene oxide–oxepin could suffer one-electron oxidation by cytochrome P450 mono-oxygenase giving (*E*,*Z*)-muconaldehyde. The observations presented may be relevant to the toxicology of benzene oxide–oxepin and other arene oxide–oxepins as we have previously shown that (*E*,*Z*)-muconaldehyde, analogously to (*Z*,*Z*)-muconaldehyde, affords pyrrole adducts with the exocyclic amino groups of the DNA bases adenine and guanine. Independent of their possible toxicological significance, the experiments described provide preparatively useful routes to (*E*,*Z*)-muconaldehyde and its congeners. Methods are also described for the trapping and analysis of reactive benzene metabolites, e.g. using the Diels–Alder reaction with the dienophile 4-phenyl-1,2,4-triazoline-3,5-dione to trap arene oxides and with the diene 1,3-diphenylisobenzofuran to trap enals.

1. Introduction

Benzene is designated a Group I carcinogen by the International Agency for Research on Cancer (Lyon, France), with acute myeloid leukemia (AML) being a potential outcome for humans who are chronically exposed to this substance [1–4]. The link between benzene exposure and leukemia is based on extensive epidemiological data [5]. This data showed that AML arose in a small number of persons who were occupationally exposed on a continuous basis to much higher levels than recommended exposure limits. Although there is no animal model for benzene-induced leukemia, experiments with mice and rats have demonstrated that benzene exposures cause tumors in a variety of organs [5].

The bewildering array of benzene metabolites and their prospective biological targets has made the definition of the molecular mechanism of benzene carcinogenesis an elusive goal. It is clear that the metabolism of benzene, primarily by cytochrome P450 2E1, gives several reactive metabolites including benzene oxide–oxepin, *ortho*- and *para*-benzoquinone (*p*-BQ), (*E*,*E*)-muconaldehyde and possibly other isomers, and benzene diol epoxide (Fig. 1). With respect to the muconaldehydes, previous studies by Ross and Witz and their coworkers have focussed on the (*E*,*E*)-isomer and its oxidative and reductive metabolism, e.g. to (*E*,*E*)-muconic acid [6] and (*E*,*E*)-6-hydroxyhexa-2,4-dienal [7], respectively. And there are perhaps additional unidentified reactive metabolites, e.g. a diepoxide derived by further oxidation of benzene oxide by cytochrome P450. Recent studies suggest that the human metabolism of benzene may be even more complex than hitherto realized: two pathways were proposed dependent on dose [8].

All of the identified electrophilic metabolites form or are expected to form adducts with glutathione, proteins and nucleic acids, and are potentially genotoxic. The major problems to solve are which of the metabolites and corresponding biomolecule adducts is/are responsible for AML and what other cancers may be initiated? Although benzene oxide is commonly regarded as a reactive benzene metabolite this epithet may only strictly apply to its facile rearrangement to phenol. Even so, the half-life of benzene oxide in blood is ca. 8 min, whilst in deuterium oxide at pD 7.0 (pD = pH + 0.4) the half-life is ca. 34 min at 25 °C [9]. The capture of benzene oxide by thiols [9] and other nucleophiles is a relatively

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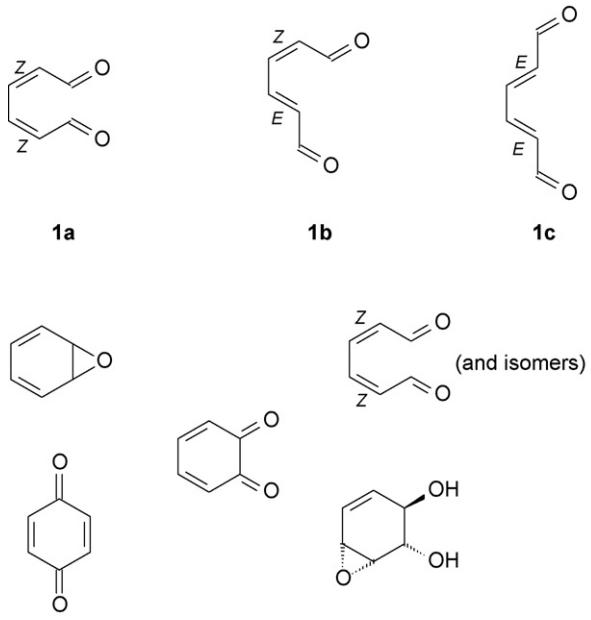


Fig. 1. Some reactive benzene metabolites.

inefficient process. Furthermore, benzene oxide may be an intrinsically unreactive epoxide because the diene π-system repels the incoming nucleophile.

Several studies have focused on the role of quinones and the related dihydroxybenzenes derived from metabolism of benzene. *p*-Benzoquinone (*p*-BQ) accumulates in the bone marrow, the site of the observed toxic effects of benzene, i.e. leukemogenicity and myelotoxicity [10]. This quinone forms adducts with nucleosides, nucleotides and DNA [11]. *p*-BQ, as well as hydroquinone (1,4-dihydroxybenzene) and catechol (1,2-dihydroxybenzene), affect the c-Myb oncoprotein, a transcription factor with an important role in hematopoiesis [12]. It was suggested that these benzene metabolites generate reactive oxygen species (ROS) that alter the c-Myb signalling pathway. Hydroquinone induces endoreduplication in cells, and hence genomic instability and carcinogenesis, by inhibiting topoisomerase II [13]. Others have focussed on *ortho*-benzoquinone from catechol and have suggested that the formation of depurinating adducts from DNA is linked to benzene leukemogenesis [14]. Another study suggested a role for nitric oxide and peroxynitrite in DNA damage induced by hydroquinone and related benzene metabolites [15].

(*E*,*E*)-Muconaldehyde has been shown to be an especially potent inhibitor of gap junction intercellular communication, the abnormal regulation of which is implicated in carcinogenesis and the blocking of hematopoiesis [16]. Our research has been focused on the isomeric muconaldehydes and benzene oxide–oxepin and, using model studies to probe their reactivities towards bimolecules. To assist the understanding of the roles of these molecules, we are developing methods for their detection and analysis using the Diels–Alder reaction.

2. Materials and methods

2.1. Safety precautions

All of the muconaldehydes and arene oxide/oxepins should be regarded as potential carcinogens and were handled with protective clothing in an efficient hood.

2.2. General procedure for the synthesis of (E,Z)-muconaldehydes

To a solution of cerium(IV) ammonium nitrate (2.01 mole equiv.) in acetone at −78 °C or acetonitrile at −40 °C was added the corresponding oxepin (1 mole equiv.) and the solution was stirred in the dark for 1 h. The resulting mixture was diluted with ice-cold diethyl ether. The ethereal solution was thrice washed with ice-cold saturated brine, dried ($MgSO_4$), filtered and concentrated to give the muconaldehyde. A similar procedure was used for iron(III) *tris*(1,10-phenanthroline) hexafluorophosphate acting on benzene oxide–oxepin.

2.3. (E,Z)-Muconaldehyde ***1b***

Yellow solid, mp 57–59 °C, lit. 58.5–59 °C [17]. ^{1}H NMR (200 MHz, CD_3CN) δ 6.21 (1H, dd, $J_{1,2}$ 7.4 and $J_{2,3}$ 11.1, H-2), 6.47 (1H, dd, $J_{5,6}$ 7.8 and $J_{4,5}$ 15.2, H-5), 7.28 (1H, dd, $J_{2,3}$ 11.9 and $J_{3,4}$ 11.6, H-3), 8.24 (1H, dd, $J_{3,4}$ 12.2 and $J_{4,5}$ 15.1, H-4), 9.77 (1H, d, $J_{5,6}$ 7.8, H-6), 10.34 (1H, d, $J_{1,2}$ 7.6, H-1).

2.4. (2E,4Z)-6-Oxo-hepta-2,4-dienal ***3***

Yellow solid, mp 42–44 °C, lit. 40 °C [18]. ^{1}H NMR (200 MHz, CD_3CN) δ 2.12 (3H, s, Me), 6.29 (1H, dd, $J_{1,2}$ 7.8 and $J_{2,3}$ 15.6, H-2), 6.40 (1H, d, $J_{4,5}$ 11.4, H-5), 6.61 (1H, dd, $J_{3,4}$ 11.2 and $J_{4,5}$ 11.8, H-4), 8.13 (1H, dd, $J_{3,4}$ 11.2 and $J_{2,3}$ 15.6, H-3), 9.60 (1H, d, $J_{1,2}$ 7.8, H-6).

2.5. (3Z,5E,)-Octa-3,5-diene-2,7-dione ***4***

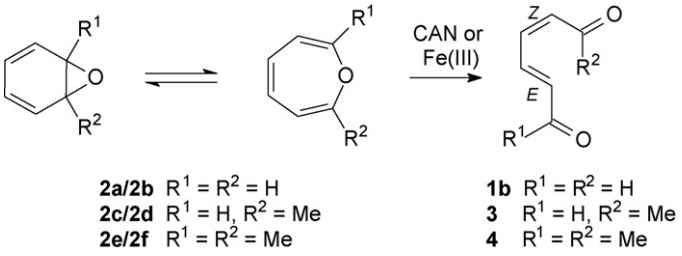
Orange solid, mp 123–125 °C, lit. 125 °C [19]. ^{1}H NMR (200 MHz, CD_3CN) δ 2.10 (3H, s, Me), 2.13 (3H, s, Me), 6.20 (1H, d, $J_{3,4}$ 15.8, H-3), 6.27 (1H, d, $J_{5,6}$ 11.4, H-6), 6.43 (1H, t, $J_{4,5 \text{ and } 5,6}$ 11.3, H-5), 7.94 (1H, dd, $J_{4,5}$ 10.8 and $J_{3,4}$ 15.7, H-4); ^{13}C NMR (50.3 MHz, CD_3CN) δ 26.64, 38.48, 124.93, 136.69, 136.89, 140.25, 198.55, 198.94.

2.6. General procedure for the reaction of enals with 1,3-diphenylisobenzofuran

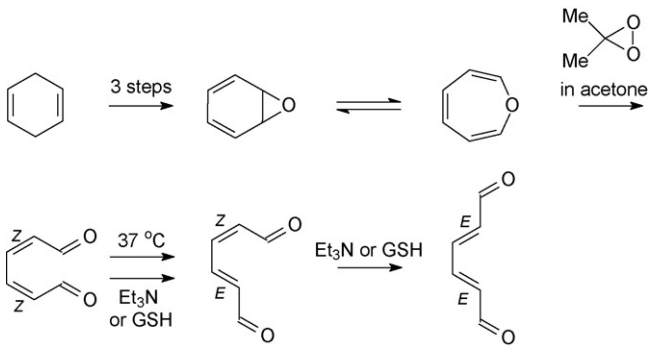
1,3-Diphenylisobenzofuran and the enal (1–2 mole equiv.) in 2,2,2-trifluoroethanol under nitrogen were heated at reflux with exclusion of light until analysis by thin layer chromatography showed completion of the reaction. The solvent was removed and the residue was purified by medium pressure chromatography on silica eluting with petrol–ethyl acetate (20:1, v/v) to give a mixture of diastereoisomeric adducts. ^{1}H NMR (200 MHz, CD_3CN) [acrolein adducts] δ 9.25 (d, CHO, isomer A), 8.94 (d, CHO, isomer B) [total 1H], 7.6 (m) 7.35 (m), 7.1 (m), 6.9 (m) [total 14H], 3.62 (m, C*H*CHO, B), 3.04 (m, C*H*CHO, A) [total 1H], 2.65 (dd, CH*H*, B), 2.49 (dd, *CHH*, A) [total 1H], 2.33 (m, C*H*H, A and C*H*H, B).

3. Conversion of benzene oxide–oxepin to muconaldehydes

One or more of the muconaldehyde isomers *Z*,*Z*, (**1a**; *E*,*Z*, **1b**; *E*,*E*, **1c**; *Z* = *cis*, *E* = *trans*) is a putative product of benzene metabolism [20]. As muconaldehydes are highly reactive dienals [9,21–23] and potentially mutagenic they may be relevant to the carcinogenicity of benzene [2–4]. In the metabolism of benzene, muconaldehydes may be derived [24,25] through the oxidation of benzene oxide–oxepin **2a**, which are established metabolites of benzene [26,27], by cytochrome P450 mono-oxygenase. To extend our earlier investigations [21,22,24,28] of the toxicology of benzenoid compounds and their metabolites, we have studied the oxidation of benzene oxide–oxepin and methyl-substituted derivatives by the one-electron oxidants cerium(IV) ammonium nitrate (CAN) and iron(III) *tris*(1,10-phenanthroline) hexafluorophosphate [29].



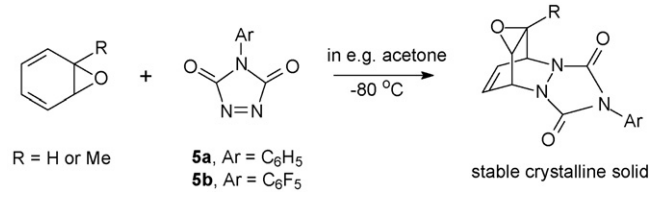
Scheme 1. Conversion of arene oxides–oxepins to (*E*,*Z*)-muconaldehydes [CAN = cericum(IV) ammonium nitrate; Fe(III) = iron(III) *tris*(1,10-phenanthroline) hexafluorophosphate].



Scheme 2. Synthetic routes to isomeric muconaldehydes.

Surprisingly, the muconaldehydes obtained were exclusively the (*E*,*Z*)-isomers.

Benzene oxide–oxepin **2a/2b** and methyl-substituted derivatives (**2c/2d** and **2e/2f**) were prepared essentially as described [9]. Reactions of **2a–2f** were performed either in acetone at −78 °C or in acetonitrile at −40 °C. Reaction of **2a/2b** with CAN gave (*E*,*Z*)-muconaldehyde **1b** (61%), which was a single diastereoisomer according to analysis by ^{1}H NMR spectroscopy. The same stereochemical outcome was observed for the oxidation of **2a/2b** by iron(III) *tris*(1,10-phenanthroline) hexafluorophosphate. Reaction

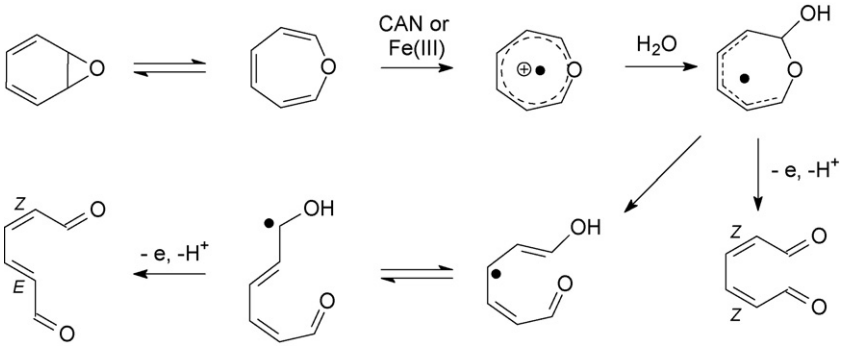


Scheme 5. Reaction of benzene oxide–oxepin and toluene oxide-2-methyloxepin with 4-phenyl-1,2,4-triazoline-3,5-dione (Cookson's dienophile, **5a**) and its pentafluoro analogue **5b**.

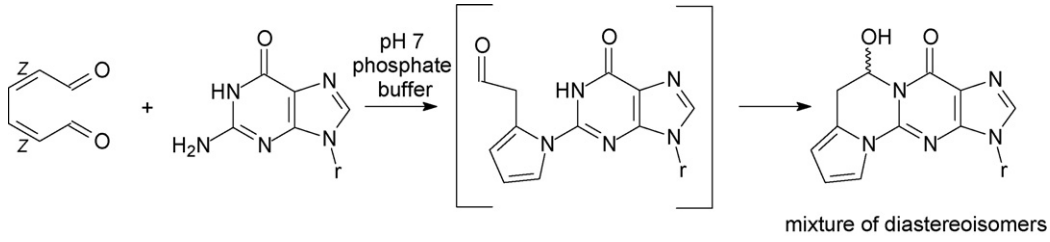
of toluene-1,2-oxide/2-methyloxepin **2c/2d** with CAN gave 6-oxo-hepta-2,4-dienal **3**, which was assigned as the (2*E*,4*Z*)-isomer, i.e. the methyl group was attached to the (*Z*)-enone component, by comparison of its ^{1}H NMR data with that reported [18]. Reaction of 1,6-dimethylbenzene oxide-2,7-dimethyloxepin **2e/2f** with CAN gave (3*Z*,5*E*)-octa-3,5-diene-2,7-dione **4**, identified by its ^{1}H and ^{13}C NMR data [30]. The oxidations described are summarized in Scheme 1.

It has been previously shown that benzene oxide–oxepin **2a/2b** is converted into (*Z*,*Z*)-muconaldehyde **1a** by oxidation with perbenzoic acid [19] or dimethyldioxirane (DMDO) [24], with the latter oxidant giving complete diastereoselectivity (Scheme 2). (*Z*,*Z*)-muconaldehyde **1a** was converted into (*E*,*Z*)-muconaldehyde **1b** by thermolysis [17,25] and into (*E*,*E*)-muconaldehyde **1c** by isomerization catalysed by triethylamine [17] or glutathione [28] (Scheme 2). Similarly, treatment of toluene-1,2-oxide/2-methyloxepin **2c/2d** with DMDO gave (*Z*,*Z*)-6-oxo-hepta-2,4-dienal, whilst 1,6-dimethylbenzene oxide/2,7-dimethyloxepin **2e/2f** afforded (*Z*,*Z*)-octa-3,5-diene-2,7-dione.

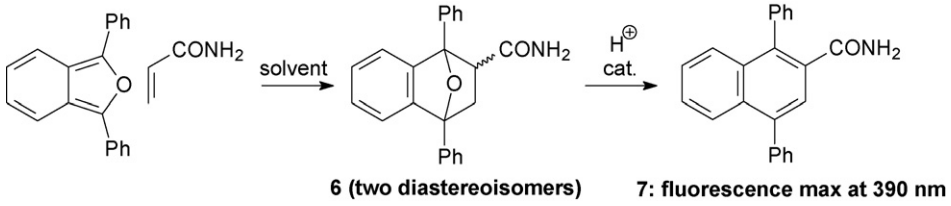
The mechanisms of the oxidations of arene oxides-oxepins (**2a–f**) by CAN and iron(III) *tris*(1,10-phenanthroline) hexafluorophosphate are presumed to be initiated by one-electron oxidation of the oxepin component. In polar media, the rapidly established equilibrium between benzene oxide and oxepin contains predominantly oxepin, the double bonds of which possess a greater nucleophilicity than those of benzene oxide [31]. Hence, the oxidation is likely to involve oxepin, which could give a radi-



Scheme 3. Putative mechanism of oxidation of **2a/2b** by CAN or Fe(III) to **1b**.



Scheme 4. Reaction of (*Z*,*Z*)-muconaldehyde with guanosine derivatives leading to pyrrole adducts (*r* = ribose or deoxyribose).



Scheme 6. Reaction of 1,3-diphenylisobenzofuran with acrylamide.

cal cation that may be captured by adventitious solvent water to afford the 2-hydroxy-2*H*-oxepin radical (Scheme 3). Ring-opening of this species gives a radical corresponding in structure to (*Z*,*Z*)-muconaldehyde. However, isomerization may occur to a radical corresponding in structure to (*E*,*Z*)-muconaldehyde, which can arise by further one-electron oxidation and deprotonation. The proposed isomerization is analogous to that of the (*E*,*E*)- and (*E*,*Z*)-pentadienyl radical. The (*E*,*E*)-isomer is more stable by ca. 10 kJ mol^{-1} with the two isomers being separated by an activation energy of ca 40 kJ mol^{-1} at 370 K for the (*E*,*Z*)→(*E*,*E*) conversion [32]. The mechanism outlined is speculative and requires further validation.

An intracellular one-electron oxidant converting benzene oxide–oxepin directly to (*E*,*Z*)-muconaldehyde could be a cytochrome P450 mono-oxygenase, acting in a similar manner to that shown by Sato and Guengerich for the oxidation of 1,2,4,5-tetramethoxybenzene [33]. The observations presented may be relevant to the toxicology of benzene oxide–oxepin and other arene oxide–oxepins as we have previously shown that (*E*,*Z*)-muconaldehyde, analogously to (*Z*,*Z*)-muconaldehyde, affords pyrrole adducts with primary amines and the exocyclic amino groups of the DNA bases adenine and guanine (Scheme 4) [21,22]. (*E*,*E*)-muconaldehyde, however, does not form such adducts because this process requires at least one double bond with *Z*-configuration. Irrespective of their possible toxicological significance, the experiments described afford preparatively useful routes to (*E*,*Z*)-muconaldehyde **1b**, (2*E*,4*Z*)-6-oxo-hepta-2,4-dienal **3** and (3*Z*,5*E*)-octa-3,5-diene-2,7-dione **4**. The latter compounds or their geometrical isomers are potential minor metabolites of toluene and *ortho*-xylene, respectively.

4. Trapping benzene metabolites

We have shown that benzene oxide can be efficiently scavenged by 4-phenyl-1,2,4-triazoline-3,5-dione (**5a**, 'Cookson's dienophile') and even better (ca. 25-fold more reactive) by its 4-pentafluorophenyl analogue **5b** [34] (Scheme 5). For the reaction of **2a**/**2b** with **5b** in tetrahydrofuran the bimolecular rate constant $k = 700$ dm^3 mol^{-1} s^{-1} and $\tau_{1/2} = 0.1$ s [34]. These reagents give stable Diels–Alder adducts (Scheme 5) that can be analyzed by high-performance liquid chromatography and mass spectrometric techniques. 4-Phenyl-1,2,4-triazoline-3,5-dione was developed for the trapping of toluene oxide in a system [35] that models the atmospheric photo-oxidation of toluene. The triazoline-3,5-diones **5a**/**5b** could, in principle, be used to trap arene oxides in metabolic systems. We have also studied the trapping of α,β-unsaturated carbonyl compounds [e.g. acrylamide, acrolein and (*Z*,*Z*)-muconaldehyde] using the reactive diene 1,3-diphenylisobenzofuran in Diels–Alder reactions (e.g. Scheme 6). The adducts **6** undergo acid-catalyzed conversion into the relatively stable naphthalene derivative **7**, which 'fixes' an α,β-unsaturated carbonyl unit [36]. Investigation of this sequence for trapping and characterizing enals is in progress.

5. Conclusions

Snyder's review [4] concluded that bone marrow disease caused by exposure to benzene could be due to one or more of the following factors: covalent binding of benzene metabolites to DNA or proteins; oxidative stress arising *via* several mechanisms; specific effects of *p*-benzoquinone and muconaldehyde. We have defined a number of possible routes to the muconaldehyde isomers and have demonstrated the propensity of the (*E*,*Z*)- and (*Z*,*Z*)-isomer to form DNA adducts. It remains to prove that (*Z*,*Z*)- and/or (*E*,*Z*)-muconaldehyde are derived from benzene oxide–oxepin by metabolic oxidation and are precursors of (*E*,*E*)-muconaldehyde. The contribution of a potential alternative pathway to (*Z*,*Z*)-muconaldehyde from dihydrocatechol needs to be appraised. Pyrrole DNA adducts from (*Z*,*Z*)- and (*E*,*Z*)-muconaldehyde (Scheme 4), still need to be evaluated as contributors to benzene carcinogenesis. Whether benzene oxide forms DNA and/or protein adducts also needs to be resolved for these processes are predicted to be inefficient.

Conflict of interest

None.

Acknowledgements

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