PAPER

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Catalytic artificial nitroalkane oxidases – a way towards organocatalytic umpolung†

Adam Pokluda, [ID] [a] Ekaterina Zubova, [ID] [a] Josef Chudoba,[b] Martin Krupička [ID] [a] and Radek Cibulka [ID] *[a]

Nitroalkane oxidases (NAOs) are flavoenzymes that catalyse the oxidation of nitroalkanes to their corresponding carbonyl compounds while producing nitrite anions. Herein, we present an artificial catalytic system using flavins or ethylene-bridged flavinium salts that works *via* an NAO-like process. Under conditions optimised in terms of solvent, base, temperature and oxygen pressure, primary nitroalkanes were transformed to aldehydes. In our system, aldehydes immediately reacted with other nitroalkane molecules to form β-nitroalcohols. The reduced flavin catalyst was re-oxidised by oxygen. An alternative mechanism towards β-nitroalcohols *via* 5-(2-nitrobutyl)-1,5-dihydroflavin was suggested through quantum chemical calculations and by trapping and characterising this dihydroflavin intermediate. Interestingly, 5-(2-nitrobutyl)-1,5-dihydroflavin is an analogue of the flavin adenine dinucleotide adduct previously observed in an NAO X-ray structure. In both mechanistic pathways, flavin-5-iminium species is formed by nitroalkanide addition to flavin. This process represents flavin-based umpolung of an original donor to an acceptor.
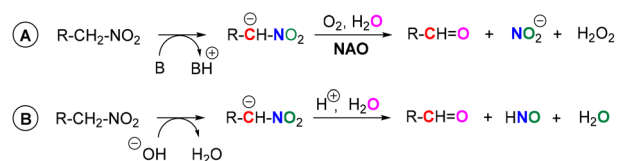
Introduction

Nitroalkane oxidases (NAOs) are enzymes with a flavin cofactor – flavin adenine dinucleotide (FAD, **1b**) – which enable the oxidative metabolism of nitroalkanes to their corresponding carbonyl compounds.[1,2] During this transformation, a nitro group is released in the form of a nitrite anion (Scheme 1A). This makes this biological process somewhat different from the transformation of chemical nitroalkane → carbonyl compound, which is called a Nef reaction.[3] In a Nef reaction, HNO (further forming nitrous oxide) is produced *via* nitro group reduction, which balances the oxidation of carbon possessing a nitro group to carbonyl function (Scheme 1B). In a NAO-mediated reaction, flavin acts as an electron acceptor, and then it is re-oxidised by oxygen, which acts as a stoichiometric oxidant being transformed to hydrogen peroxide.[1]

A key step in the mechanism of NAOs is flavin-N(5)-adduct formation through nucleophilic attack of a nitroalkanide on a flavin moiety (Scheme 2A).[1,4] This is followed by nitrite anion release, which forms electrophilic iminium species. Thus, a change in the polarity (umpolung[5]) of the nitroalkanide nucleophile is accomplished. The iminium species readily undergo the addition of a nucleophile,[6] like deprotonated water, in a reaction leading to a carbonyl compound. The product of another nitroalkanide addition – "5-nitrobutyl-flavin"‡ – has been observed by X-ray diffraction as a stable form of FAD in NAO (see Scheme 2B).[1,7] In another study, cyanide adduct formation was used to prove the presence of an iminium species.[8] Finally, a tetrahedral adduct of a nucleophile splits and releases an aldehyde and a reduced flavin.

The interaction of a nitroalkanide with a flavin resulting in a carbonyl compound and reduced flavin in an artificial system was first reported by Yano.[9] Later, Foss and others utilised nitrite, produced from nitromethane in a catalytic process using ethylene-bridged flavinium salt **2**, as a nontoxic source of nitrogen dioxide for the stoichiometric agent in the

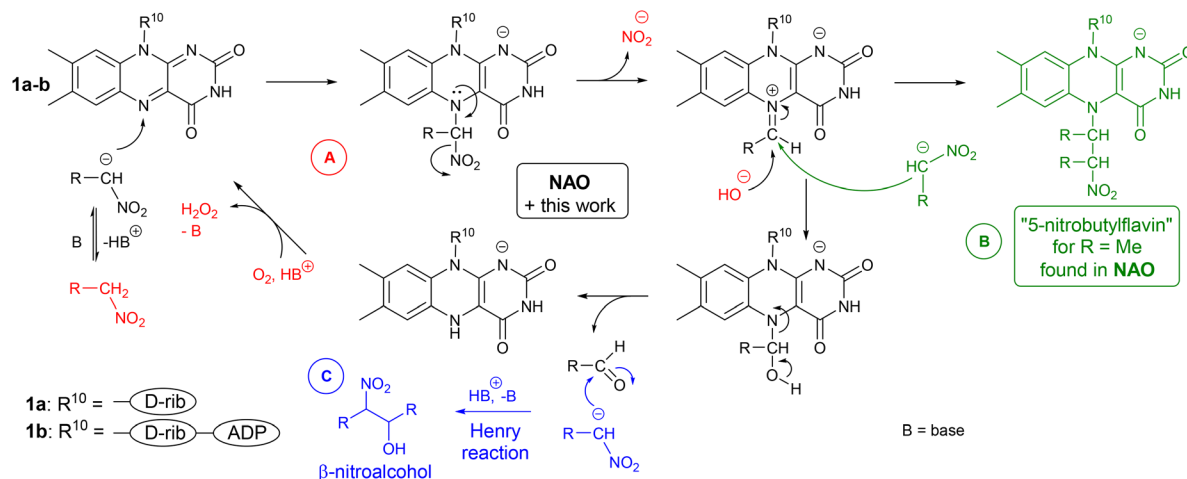**Scheme 1** Conversion of nitroalkanes to carbonyl compounds (A) by NAO and (B) *via* Nef reaction.

[a]Department of Organic Chemistry, University of Chemistry and Technology, Prague, Technická 5, 166 28 Prague, Czech Republic. E-mail: cibulkar@vscht.cz
[b]Central Laboratories, University of Chemistry and Technology, Prague, Technická 5, 166 28 Prague, Czech Republic

‡ "5-nitrobutylflavin" is a simplified name for 5-(2-nitrobutyl)-1,5-dihydroflavin used in the literature for an FAD analogue found in NAO.

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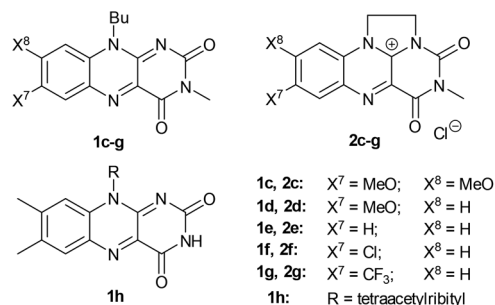This journal is © The Royal Society of Chemistry 2023

Scheme 2 (A) Catalytic cycle in NAO based on a flavin cofactor, (B) formation and structure of 5-nitrobutylflavin, and (C) Henry reaction observed in an artificial system.

oxidation of alcohols and ethers catalysed by TEMPO.[10] Recently, Lupidi, Palmieri and Petrini[11] reported a tandem process where a nitroalkane was converted to an aldehyde using riboflavin (**1a**), which was followed by a Henry reaction[12] with another nitroalkane anion (Scheme 2C) to form β-nitroalcohol. There, two equivalents of riboflavin **1a** relative to the substrate were used.

Herein, we present a fully catalytic biomimetic process based on flavin derivatives **1** or **2** providing β-nitroalcohols in good preparative yields from the corresponding nitroalkanes *via* NAO-like umpolung of nitroalkanes (Scheme 2A). Experimental studies and quantum chemical calculations provided evidence for the possible employment of 5-(2-nitroalkyl)-1,5-dihydroflavin (*cf.* Scheme 2B) as an alternative pathway to that traditionally described for NAO.

1c, 2c: X^7 = MeO; X^8 = MeO
1d, 2d: X^7 = MeO; X^8 = H
1e, 2e: X^7 = H; X^8 = H
1f, 2f: X^7 = Cl; X^8 = H
1g, 2g: X^7 = CF₃; X^8 = H
1h: R = tetraacetylribityl

Results and discussion

Development of an artificial catalytic NAO-like system

In both natural and artificial systems, flavins are known to be easily re-oxidised from their reduced form by oxygen.[13,14] Thus, we suspected that a catalytic amount of a flavin derivative might be sufficient to transform nitroalkanes to β-nitroalcohols. To achieve this, we decided to optimise the reaction conditions using nitroethane (**3a**) as a model sub-

Table 1 Selected optimization data for the organocatalytic transformation of nitroethane (**3a**) to **4a** mediated by **2c**[a]

Entry	Base	Atmosphere	Temp. (°C)	Reaction time (h)	**3a** converted to **4a**[b] (%)
1	Bu₄N⁺ OH⁻	O₂ (2.5 atm)	25	16	46
2	Na₂CO₃	O₂ (2.5 atm)	25	16	54
3	Et₃N	O₂ (2.5 atm)	25	16	56
4	—	O₂ (2.5 atm)	25	16	0
5	Et₃N	Ar	25	16	15
6	Et₃N	O₂ (1 atm)	25	16	52
7	Et₃N	O₂ (4.5 atm)	25	16	68
8	Et₃N	O₂ (4.5 atm)	5	16	43
9	Et₃N	O₂ (4.5 atm)	45	2	61
10[c]	Et₃N	O₂ (4.5 atm)	45	2	5

[a] Reactions were performed with 0.6 mmol of nitroethane (**3a**) in tempered and pressurized Schlenk tubes with 0.55 equiv. of base, 10 mol% of **2c** and 1 mL of water as a solvent. [b] Determined by ^{1}H NMR using dimethyl sulfone as a standard. [c] In the absence of catalyst.

strate (Table 1). First, we used ethylene-bridged 7,8-dimethoxy-3-methyl flavinium chloride (**2c**) as a flavin catalyst. Ethylene-bridged salts **2** have been previously shown to likely form adducts with nucleophiles due to a positive charge.[15] In our previous study,[16] 7,8-dimethoxy derivative **2c** was shown to be the most stable one among flavinium salts **2**; **2c** is also stable under slightly basic conditions and readily soluble in water.

Inspired by a protocol for the reaction with a stoichiometric amount of riboflavin,[11] we used 0.55 equiv. of base relative to the substrate and 1 mL of water as a solvent for 0.6 mmol of **3a**. On the other hand, we used only 10 mol% of flavin catalyst. The reactions were performed in Schlenk tubes pressurised using oxygen to 2.5 atm and at 25 °C for 16 h. The course of the reaction was monitored using ^{1}H NMR. The first set of

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experiments (entries 1–5 and ESI S1.7.1†) unambiguously showed that the reaction proceeds in a catalytic manner under oxygen since more than 20% of **3a** was converted to β-nitroalcohol **4a**, keeping in mind the stoichiometry of the reaction. In the absence of oxygen (under argon), the flavin catalyst did not regenerate, which resulted in a conversion of less than 20% (entry 5). Regarding base, it is critical for the reaction (*cf.* entry 4). Sodium carbonate and triethylamine were found to be more suitable than tetrabutylammonium hydroxide. However, we observed product loss after 8 hours using sodium carbonate (Fig. 1), which is probably caused by a retro-Henry reaction[3d] followed by nitroalkane decomposition (see the Mechanistic studies below for details). On the other hand, product loss was not observed when triethylamine was used, so this base was selected for further investigation. The other tested organic and inorganic bases showed worse performance (see ESI S1.7.1†). We also found that a higher oxygen pressure (4.5 atm) was not essential but helpful (*cf.* entries 4, 6 and 7) and a higher temperature (45 °C) significantly shortened the reaction time to 2 hours (*cf.* entries 7–9 and Fig. 1). Although the yield at 45 °C after 2 hours was slightly lower than that with a longer time and at 25 °C, we chose the higher temperature and shorter time for further experiments to overcome the potential problem of low solubility of more lipophilic substrates. It is important to note that only a trace amount of product was formed in the control reaction performed without any catalysts (entry 10).

Under the best conditions identified above, we tested other flavinium salts **2** and received similar results, with the exception of the electron-poor derivative **2g** possessing a trifluoromethyl group (Table 2). Then, we considered whether other flavin derivatives could be analogously used in the catalytic transformation of **3a** to **4a**. To our delight, we found that riboflavin derivatives **1d–1g** and riboflavin tetraacetate§ (**1h**) are good catalysts of this reaction. On the other hand, alloxazine and deazaflavin derivatives **5** and **6**, and electron-rich dimethoxyflavin **1c** were inefficient. As for the neutral catalysts

Table 2 Organocatalytic nitroethane (**3a**) transformation to **4a** based on various flavin derivatives[a]

Catalyst	3a converted to 4a[b] (%)	
	In water	In water/DMSO (1 : 2 v/v)
1c	—	15
1d	—	45
1e	—	50
1f	45	61 (69[c])
1g	—	51
1h	—	60
2c	61	35
2d	51	—
2e	66	36
2f	64	—
2g	41	—
5	—	11
6	—	10

[a] Reactions were performed with 0.6 mmol of nitroethane in a Schlenk tube tempered at 45 °C and pressurized with O_2 at 4.5 atm using 10 mol% of catalyst and 0.55 equiv. of Et_3N in 1 mL of solvent. Reaction time was 4 h. [b] Determined by ^{1}H NMR using dimethyl sulfone as a standard. [c] 1.1 equiv. of Et_3N.

1, **5** and **6**, a water/DMSO (1 : 2) mixture was used for their complete solubility. Interestingly, the flavinium catalysts were significantly less efficient in the water/DMSO mixture (see ESI S1.7.3 and S1.7.4†) and in the mixtures of water with other solvents (see ESI S1.7.2† for data on other solvents). Therefore, for further studies, we selected **2c** in water as a representative of a catalytic system in a purely aqueous environment (method A). Regarding the neutral flavins, we selected a system with 7-chloro derivative **1f** in a mixture of water/DMSO (1 : 2). Finally, we used 1.1 equivalents of base (Et_3N) in the case of **1f**, which was found to be beneficial (method B).

In preparative experiments, the selected methods were applied to other nitroalkanes. While method A, with flavinium salt **2c** in water, was used for relatively hydrophilic nitroethane (**3a**) and nitromethane (**3b**), method B, with flavin **1f** in a water/DMSO mixture, was used for water-insoluble substrates to take advantage of the solubilising properties of DMSO (Table 3). For primary nitroalkanes, consistent preparative yields of β-nitroalcohols **4** of approximately 60% were obtained; with 5 mol% of catalyst **1f**, the reaction produced a slightly reduced
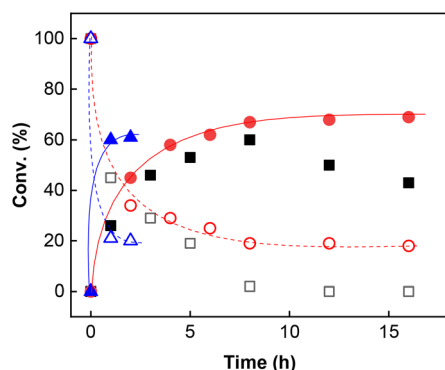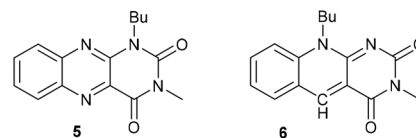

Fig. 1 Reaction course of transformation of 0.6 mmol of **3a** (empty symbols) to **4a** (filled symbols) mediated by **2c** (10 mol%) under oxygen (4.5 atm) in 1 mL of water. Squares: sodium carbonate used as a base at RT; circles: Et_3N used as a base at RT; triangles: Et_3N used as a base at 45 °C.

§ Riboflavin tetraacetate can be readily obtained by a one-step procedure from commercially available riboflavin (vitamin B2).

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Table 3 Examples of nitroalkane **3** transformations in a preparative scale

Entry	Nitroalkane	Product[a]	Method	Yield (%)
1	H₃C—NO₂ **3b**	—	A	0
2	H₃C—NO₂ **3a**	**4a**	A[b]	62
3	**3c**	**4c**	B[b]	61
4	**3d**	**4d**	B[b]	57
5	**3e**	—	B	0
6	Ph **3f**	**4f**	B[b]	59
7	Ph **3f**	**4f**	B[b,c]	40
8	**3d** + **3f**	**4d/4f** **4g** / **4h**	B	9/34/57[d]
9	Ph **3g**	**7**	B	52

[a] 2 mmol of substrates **3a–g** were treated in a Schlenk tube pressurized with O₂ at 4.5 atm. Products were isolated by column chromatography. [b] Product was obtained as a mixture of diastereomers at ratios from 40:60 to 30:70. [c] 5 mol% of **1f**. Method A: Used 10 mol% of catalyst **2c** and 0.55 equiv. of Et₃N in water. Reaction performed at 25 °C for 20 h. Method B: Used 10 mol% of catalyst **1f** and 1.1 equiv. of Et₃N in a wa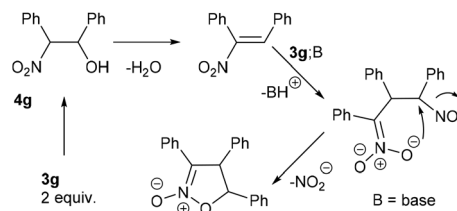ter/DMSO (1:2) mixture. Reaction performed at 45 °C for 4 h. [d] Ratio of products (**4f/4d/4g + 4h**) obtained by LC-MS analysis.

yield of **4f** from **3f**. 2-Nitropropane (**3e**) as a representative of the secondary substrate did not react at all and only the starting material is observable in the reaction mixture. With nitromethane (**3b**), we observed the formation of a complex mixture of products. On the other hand, we confirmed the presence of formaldehyde as a product of **3b** umpolung (see ESI S2.3†). Most likely, formaldehyde is very reactive, providing products of its multiple reactions with nitromethane.
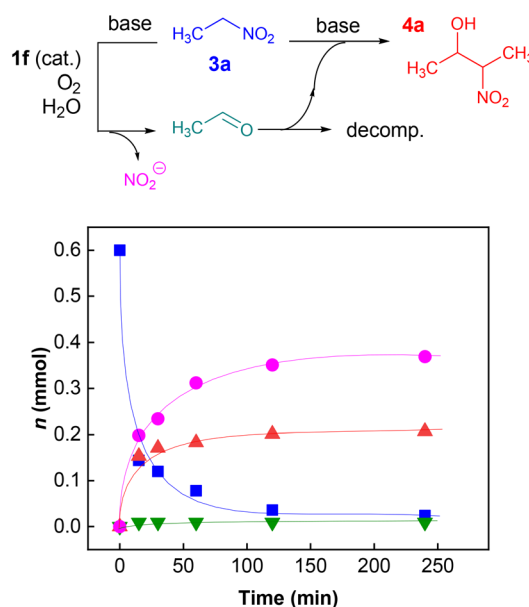
The reaction of different primary nitroalkanes **3d** and **3f** together under the optimal conditions provided a mixture of four products (Table 3, entry 8 and ESI S2.4†). The use of (nitromethyl)benzene (**3g**) produced a different product than the expected one, as the primarily formed β-nitroalcohol **4g** probably underwent elimination of water and subsequent Michael addition with a third nitroalkanide anion to give a five-membered ring product **7**, as described in the literature[11] (Table 3, entry 9, Scheme 3).

Mechanistic studies

To elucidate the overall reaction scheme of nitroalkane → acetaldehyde transformation followed by a Henry reaction, we

Scheme 3 Mechanism of (nitromethyl)benzene **3g** "trimerization" to product **7**.

monitored the main reaction products/intermediates in an experiment using 0.6 mmol of nitroethane in the presence of 10 mol% of **1f** (see Fig. 2). We used Griess colorimetry[17] to quantify the nitrite anions formed in our reaction, thus confirming the NAO-like process. In an NAO-mediated reaction producing an aldehyde, irreversible formation of NO₂⁻ is quantitative with regard to the starting nitro compound amount. However, in the case of the subsequent Henry reaction, there should be only half the amount of NO₂⁻ formed in theory (i.e. 0.3 mmol). In the experiment, we observed the formation of ca. 0.4 mmol of nitrite, which is higher than the maximal amount, considering the quantitative conversion of **3a** to **4a**. This is probably due to the fact that the acetaldehyde produced by the NAO-like process does not completely undergo the Henry reaction, but it is particularly decomposed via self-condensation under basic conditions. The amount of free acetaldehyde was only around 1.5% for the whole time. It is likely that acetaldehyde decomposition is relatively fast. In a similar experiment with **3f**, more stable and non-volatile phe-

Fig. 2 Reaction course of transformation of 0.6 mmol of **3a** (squares) to **4a** (up-triangles) mediated by **1f** (10 mol%) under oxygen (4.5 atm) at 45 °C in 1 mL of water/DMSO (1:2) mixture. Amounts of nitrite (circles) and acetaldehyde (down-triangles) are given.

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nylacetaldehyde was found in an amount slightly below 10% (see ESI S2.2†). It should be noted that only traces of carboxylic acid were detected by mass spectroscopy in the reaction mixture (see ESI S2.2†). It means that oxidation of aldehydes is not favourable under our conditions. The aldehyde oxidation did not take place even under irradiation which was proved by an independent experiment (see ESI S2.5†). Thus, aldehydes not consumed by subsequent Henry reactions seem to be the major by-products of the nitroalkane transformations.

In addition to the reaction scheme *via* aldehyde formation and its reaction with nitroalkanes, another reaction pathway to β-nitroalcohol products proceeding through the 5-(2-nitroalkyl)-1,5-dihydroflavin intermediate (F or L, see Fig. 3)

could be considered. It can be formed if a nitroalkanide attacks an iminium species (C or J) instead of water/hydroxide. Both the reaction pathways were evaluated using quantum-chemical calculations for flavin **1f** and flavinium **2c** catalysts, confirming their feasibility from a thermodynamic point of view (see ESI S1.9† for details). For flavinium salts **2**, we expected β-nitroalcohols to be released from F through substitution with hydroxide. The dihydroflavin formed is then re-oxidised by oxygen to form a flavinium ion, as is known from several applications of flavinium salts in oxygenation reactions.[13] In the case of neutral flavins **1**, consideration should be given to an alternative pathway involving the oxidation of L to the corresponding 5-alkylflavinium salt M, which might be
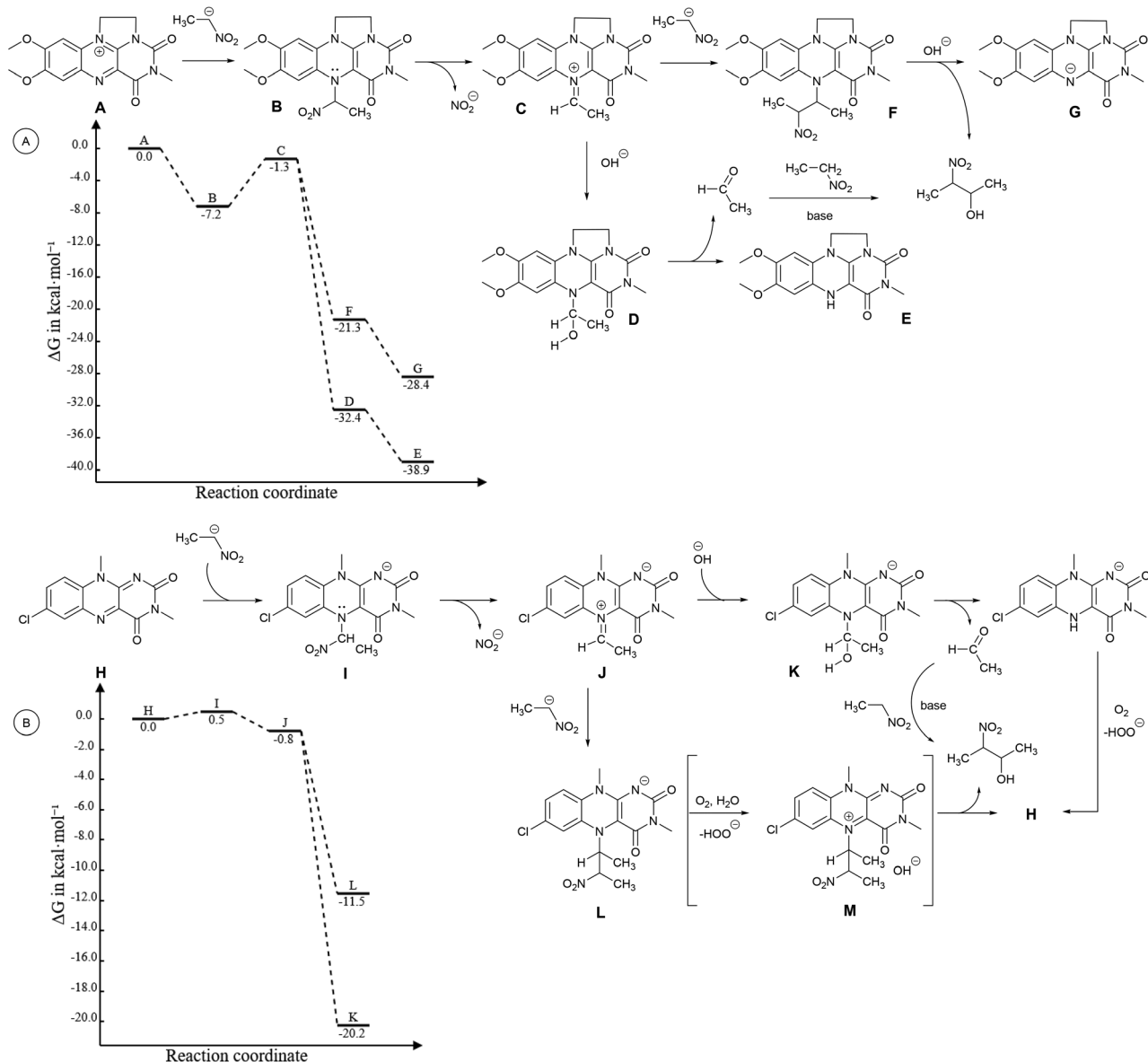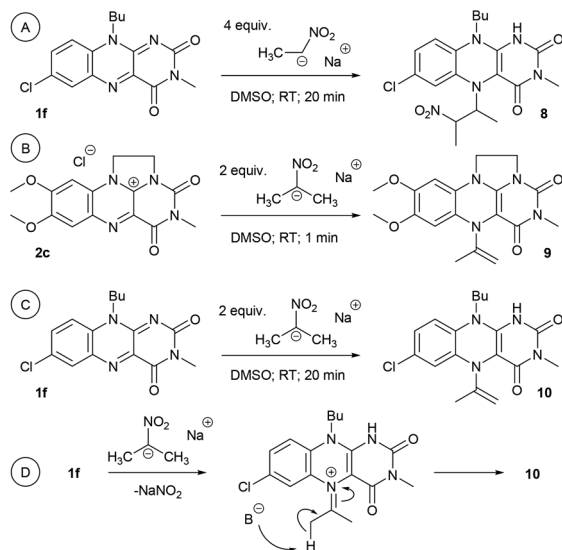

Fig. 3 First part of the catalytic transformation of **3a** to **4a** mediated (A) by **2c** and (B) by the 10-methyl analogue of **1f** as a series of elementary steps, considered for computational studies. Diagrams for reactions are given. The geometries and Gibbs free energy contributions have been calculated at the B3LYP[19]/def2-TZVP[20] level, solvation free energy contributions using the CPCM[21] formalism and parameters for DMSO. Energies have been calculated using the DLPNO-CCSD(T)[22] method with def2-QZVP[20] basis. Counterions are omitted.

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Scheme 4 (A) Formation of adduct **8** from **1f** and sodium 1-nitroethan-1-ide; (B) adduct **9** from **2c** and sodium 2-nitropropan-2-ide; (C) adduct **10** from **1f** and sodium 2-nitropropan-2-ide and (D) the corresponding intermediate. See ESI S2.6† for characterization.

dealkylated using a hydroxide/water nucleophile, analogous to procedures described in the literature.[18] It is likely that both reaction pathways are involved in the catalytic transformation of nitroalkanes to β-nitroalcohols in a water or water/organic medium, particularly in the case of neutral flavins **1**. This interpretation was supported by our observation of adduct **8** formation as a result of the interaction of **1f** with sodium 1-nitroethan-1-ide (Scheme 4A). Adduct **8** was fully characterised using NMR and HR-MS techniques, and it represents an artificial analogue of nitrobutyl-FAD found in NAO.[7] We also attempted to characterise the primary adducts of nitroalkanide anions with a flavin or flavinium catalyst, but were not successful when using 1-nitroethan-1-ide, probably because of the high reactivity of the corresponding iminium salt formed by its addition to flavin and the release of nitrite. However, we were able to observe and fully characterise the 2-nitropropan-2-ide adducts **9** and **10** as being in enamine form (Schemes 4B–D). This may be why the secondary nitroalkane does not undergo any umpolung with flavin and, consequently, does not provide a product after a Henry reaction.

Conclusions

Our study clearly showed that flavin derivatives can enable nitroalkane transformation to aldehydes using a catalytic procedure analogous to that occurring with NAO[1,2] *via* N(5)-adduct formation with a flavin derivative, producing nitrite and hydrogen peroxide. Under our optimized reaction conditions, the resulting aldehyde readily undergoes the Henry reaction with a second nitroalkane molecule to form a β-nitroalcohol. Using quantum chemical calculations and the isolation of intermediates, we documented an alternative

pathway to β-nitroalcohols *via* nitroalkanide attack on a flavin-iminium intermediate. Importantly, 5-(2-nitrobutyl)-1,5-dihydroflavin, a product of this attack, is an analogue of stable FAD form revealed in NAO by X-ray crystallography.[7] We generated and fully characterised it in an artificial system. The results of this study may provide inspiration for other mechanistic studies of NAO-based transformations.

Our system for the transformation of nitroalkanes to β-nitroalcohols is catalytic, distinguishing it from previous systems that used more than stoichiometric amounts of riboflavin. Our procedures were based not only on electrophilic flavinium salts **2** but also, most importantly, on neutral flavins **1**, which are derivatives of flavin cofactors. From the point of view of flavin-based catalysis, the presented system is the first artificial catalytic system using the flavin-N(5) position to enable C–C bond formation. It is also an artificial example of noncanonical covalent reactivity of flavins.[23]

We have shown that NAO-like umpolung of nitroalkanes (typically reacting as donors) to any electrophilic species like aldehydes or iminium salts can be used in a catalytic way in an artificial system through various flavin derivatives. The general usage of such a system to change the polarity of reagents can be assumed and is now under investigation in our laboratories.

Author contributions

R. C., A. P. and E. Z. wrote the paper with input from all the authors. A. P. and E. Z. performed the entire synthesis of all used compounds and catalytic experiments. Analysis by mass spectrometry was performed by J. C. E. Z. and M. K. conducted the computational studies. Experimental data were analysed by A. P. The project was conceived by R. C.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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