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Inverse kinetic isotope effect in Magtrieve™ mediated oxidation or deoximation of benzaldoxime: mechanistic implication

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ABSTRACT

Magtrieve™ (CrO_2) mediated reactions with benzaldoxime (**1a**) and its deuterium congener (*d*-**1a**) led to the observation of inverse deuterium kinetic isotope effect (i-DKIE) for the substrate's oxidation (Eq. 1a) as well as deoximation (Eq. 2a) process. Disappearance of the starting material **1a** and formation of the products—1,3-dipolar cycloaddition product (**4a**) as well as benzaldehyde (**3a**)—followed a typical 1st-order kinetics. The observed k_D/k_H values, in the range of 2–4, suggest for a strong secondary isotope effect which was further evidenced by the fact that d-labeling was retained in **3a**. Therefore, the observed i-SDKIE supports our original hypothesis that aldoxime (with sp^2-C) interacts with CrO_2 in a rate determining step to form a tetrahedral (now with sp^3-C) structure, possibly like **6**, which may act as a common intermediate for both the pathways.

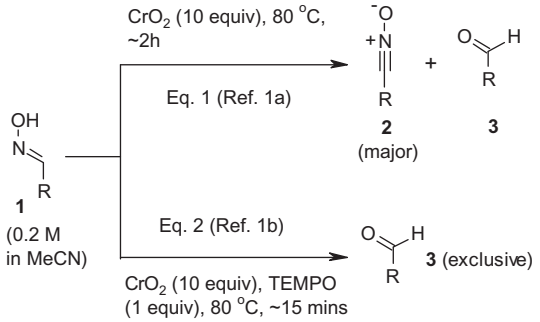
Recently, we have demonstrated that Magtrieve™ (CrO_2) is an effective oxidizing agent for the conversion of aldoxime (**1**) to nitrile oxide (**2**), a versatile intermediate in organic synthesis.[1a] Often, minor amount of aldehyde (**3**) is also formed as a result of deoximation of the aldoxime. Subsequently, we have reported that, such reaction course is strongly perturbed in the presence of a stable radical like TEMPO yielding the aldehyde as an exclusive product.[1b] From the latter study, it is inferred that, a radical pathway might be involved in the oxidation process, whereas, the deoximation reaction could be explained by a kind of disproportion of a CrO_2·aldoxime adduct. Results from our previous studies are summarized in Scheme 1. Subsequently, we endeavored to investigate deuterium kinetic isotope effect (DKIE)[2,3] in these reactions (Eqs. 1 and 2).

In this Letter, we communicate our new observation of large inverse secondary deuterium kinetic isotope effect (i-SDKIE)[4] in both the type of reactions: (i) oxidation to nitrile oxide (Eq. 1), and (ii) deoximation to aldehyde (Eq. 2).

Benzaldoxime (**1a**) and its congener *d*-benzaldoxime (*d*-**1a**) were chosen to study the kinetics (Scheme 2). Initial experiments were carried out following our previously reported standard condition, that is, using 10 mol equiv of CrO_2 as oxidizing agent, and heating at 80 °C in MeCN solvent (0.2 M with respect to aldoxime).[1] As benzonitrile oxide (**2a**) is not practical to isolate, formation of the corresponding 1,3-dipolar cycloaddition product **4a** was considered as a surrogate to monitor the progress of nitrileoxide formation.

During the early trials, following two observations were made. Firstly, the use of *d*-**1a** consistently led to faster reactions—both for Eqs. 1a and 2a—indicative of i-DKIE (reactions monitored by TLC as well as by HPLC). Secondly, aldehyde—the deoximation product—retained the deuterium label, indicating for a SDKIE (confirmed by comparing Mass, and NMR spectra with an authentic compound).

Subsequently, for all kinetic experiments, reactions were set as per our reported procedure[1] with the changes that 0.1 M aldoxime concn, and 1.0 equiv TEMPO were used (Scheme 2).[11,12] Progress of the reactions was monitored by taking aliquots at different time points, and quantifying the starting materials and products by HPLC. Representative chromatographic profile for the reactions as depicted in Eqs. 1a and 2a is presented in Figure 1a and b. Detailed



Scheme 1. Effect of TEMPO in CrO_2 mediated oxidation of aldoximes.

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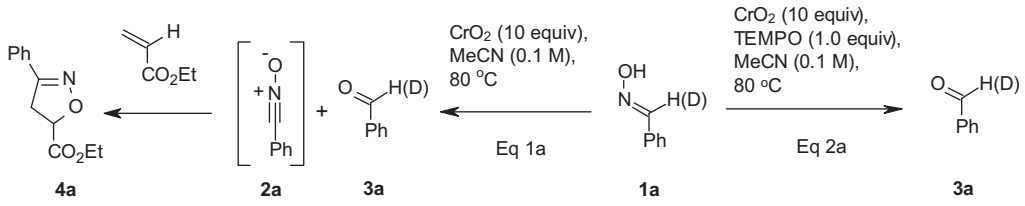

Scheme 2. Reactions chosen for studying kinetic isotope effect.

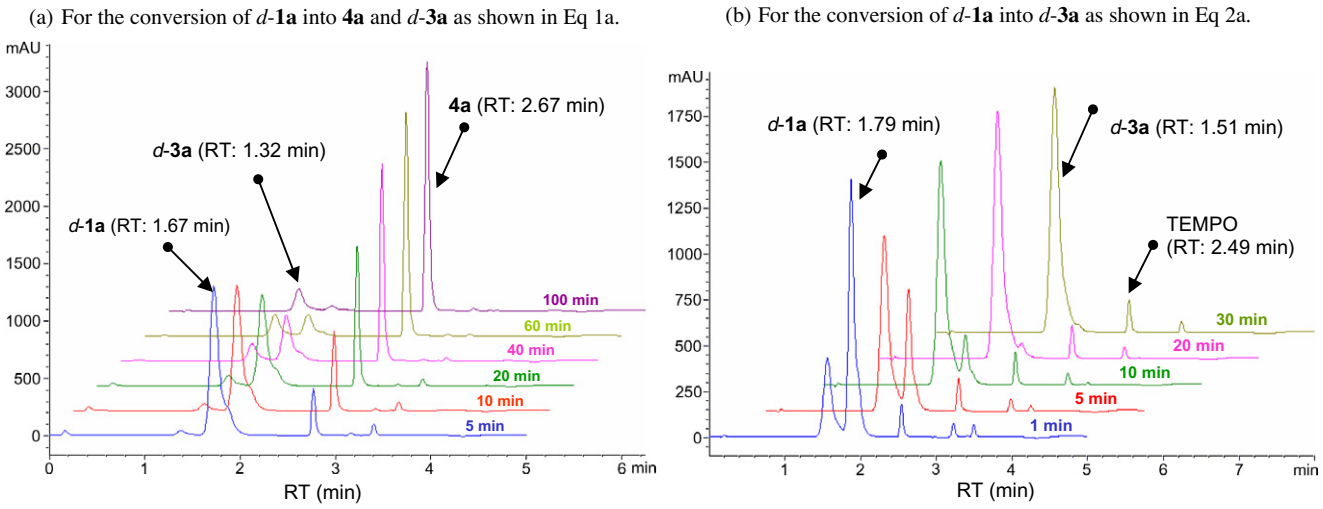

Figure 1. Representative chromatograghic profile to monitor progress of the reactions as depicted in Scheme 2. Corresponding HPLC signals for the starting material **1a** (*d*-**1a**) and for the products **3a** (*d*-**3a**) and **4a** were characterized by HPLC-Mass as well as by matching with the authentic compounds.[13,14] At each time point, 100 μL of aliquot was withdrawn from the reaction mixture (0.1 M with respect to starting concn of **1a**; initial solvent content of 8.2 mL), which was then diluted by 10 times, before injecting 2.0 μL of latter stock solution into HPLC for analysis using UV detector (λ_{max} set at 260 and 245 nm for Eqs. 1a and 2a, respectively).[11,12] Detailed HPLC conditions and protocols are given as Supplementary data.

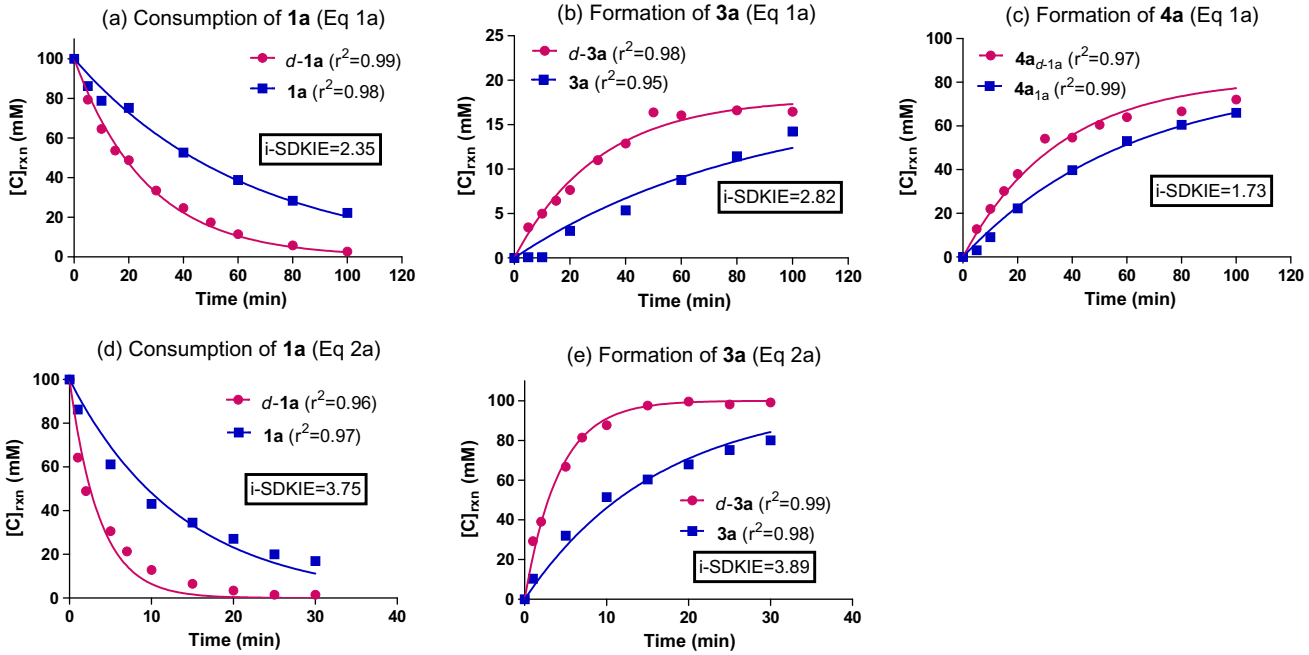

Figure 2. Kinetic plots for Eqs. 1a and 2a. Real time concentration of starting materials **1a** (*d*-**1a**) and products **3a** (*d*-**3a**) and **4a** were derived from the observed area under the HPLC signals as exemplified in Figure 1 followed by quantification based on HPLC comparison with the authentic compounds. For detailed HPLC analysis, Supplementary data is referred. Plots were generated using PRISM (GraphPad Software). Best fit non-linear curves were obtained using one phase decay equation: $Y = (Y0 - Plateau) * \exp(-k * t) + Plateau$; *Y* is [C]rxn in mM; *t* is time in min; Y0 is *Y* at 0 min; *k* is the rate constant. For Eq. 1a, graph parameters: (i) Y0 = 100 mM and Plateau = 0 mM for **1a** (based on 100% consumption); (ii) Y0 = 0 mM and Plateau = 82 mM for **4a** (based on a max of 82% yield); (iii) Y0 = 0 mM and Plateau = 18 mM for **3a** (based on a max of 18% yield). For Eq. 2, graph parameters: (i) Y0 = 100 mM & Plateau = 0 mM for **1a** (based on 100% consumption); (ii) Y0 = 0 mM & Plateau = 100 mM for **3a** (based on a max of 100% yield).