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First definitive spectroscopic evidence for a stable intermediate in a sulfinyl-transfer reaction: reaction of dibenzo[1,2]oxathiin-6-oxide with sodium ethoxide in anhydrous ethanol†

Ik-Hwan Um,* Myung-Jin Kim and Hye-Won Lee

Department of Chemistry, Ewha Womans University, Seoul 120-750, Korea. Tel: 822 3277-2349, Fax: 822 3277-2844, E-mail: ihum@mm.ewha.ac.kr

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The UV spectral changes along with the kinetic results for the title reaction suggest that the reaction proceeds through a rapidly formed stable intermediate which decomposes slowly to the product.

Acyl-transfer and related reactions such as phosphoryl- and sulfonyl-transfer reactions are central to our understanding of biochemical pathways. Consequently, there has been considerable interest in examining this large class of reactions.[1–11] Acyl-transfer reactions may proceed either through a stepwise mechanism with an addition intermediate or through a concerted mechanism, depending upon the nature of the nucleophile and structure of the substrate.[1–11] For example, it has generally been understood that reactions of esters with amines proceed through a stepwise mechanism, in which the rate-determining step (RDS) changes from breakdown to formation of the intermediate as the attacking amine becomes more basic than the leaving group by 4–5 pK_a units.[2–4] However, the corresponding reactions with anionic nucleophiles are still controversial.[5–11]

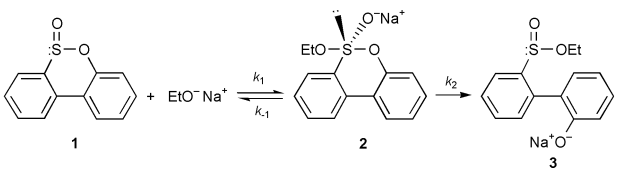
Buncel *et al.* have suggested that acyl-transfer reactions proceed through a stepwise mechanism, based on Hammett plots obtained from reactions of a series of substituted phenyl acetates, phosphinates and sulfonates with anionic nucleophiles.[5,6] Recently, Okuyama *et al.* arrived at a similar conclusion for buffer catalyzed hydrolysis of sulfinate esters.[7] By contrast, Williams *et al.* have concluded that acyl-transfer reactions with anionic nucleophiles proceed through a concerted mechanism, based on linear Brønsted-type plots obtained from reactions of *p*-nitrophenyl acetate and related phosphinate and sulfonate esters with a series of substituted phenoxides.[8] The cross interaction correlations of Jencks,[9] isotope effect studies by Hengge[10] and Marcus analysis by Guthrie[11] have all supported the concerted process.

However, there has been no definitive evidence such as spectroscopic data for any intermediate. We now report, along with kinetic evidence for a stepwise mechanism, the first spectroscopic observation of an intermediate in the reaction of a sulfinate ester (**1**, dibenzo[1,2]oxathiin-6-oxide) with EtONa in anhydrous EtOH, as shown in Scheme 1.

Fig. 1 shows UV spectral changes for the reaction of **1** with EtONa in EtOH. The first spectrum from the top has been taken from the substrate alone in EtOH, and the next ones have been recorded immediately after addition of EtONa at intervals of 180 s. The time between the first and the next spectrum is less than 3 s, but even with this short period the spectral change between the two is significant. Furthermore, there is no isosbestic point discernable in the UV spectra. In subsequent experiments with different concentrations of EtONa, a similar result is found, *i.e.* rapid spectral change upon addition of nucleophile followed by slow modification of the spectrum, but the initial spectral change becomes more significant with increasing concentration of EtONa. Such spectral changes, as well as the absence of isosbestic points, definitely suggest that the present reaction proceeds through rapid formation of a stable intermediate which decomposes slowly to the product.

The initial spectral change has been followed using a stopped-flow spectrophotometer and is illustrated in Fig. 2. These spectral changes were monitored for 16 ms at an interval of 2 ms. Two isosbestic points are observed in Fig. 2, indicating that there is no stable intermediate during this fast process. Therefore, based on the spectroscopic data, it is proposed that the present reaction proceeds in two steps with rapid formation of an intermediate shown as **2**, that decomposes slowly to the product **3**,[12] as shown in Scheme 1.

Further support for the stepwise mechanism can be provided by determination of the microscopic rate constants, k_1, k_{-1}, and k_2 in Scheme 1. Therefore, a kinetic study was performed to determine the k_1 value in Scheme 1 using a stopped-flow technique under pseudo-first-order conditions. The plot of pseudo-first-order rate constants (k_{obs}) *vs.* the concentration of EtONa exhibits good linearity with a large positive intercept (Table 1, ESI†). In a separate control experiment, **1** was shown to be inert in EtOH in the absence of EtONa, indicating that the positive intercept in the plot of k_{obs} *vs.* [EtONa] cannot be ascribed to ethanolysis of **1**, but represents the reverse reaction, k_{-1}. Therefore, the microscopic rate constants (k_1 and k_{-1}) of



Scheme 1

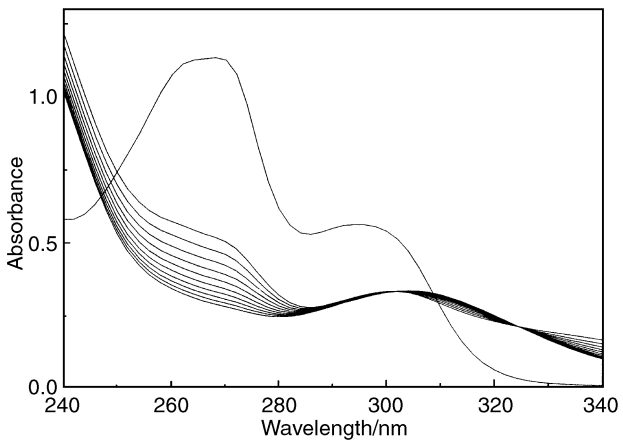


Fig. 1 Repetitive scanning of the UV spectra for the reaction of **1** with EtONa (**1** ⇌ **2** → **3**) in anhydrous EtOH at 25.0 ± 0.1 °C. [**1**] = 7.50×10^{-5} M, [EtONa] = 12.1×10^{-3} M. Time interval less than 3 s for the first and second spectrum from the top, and 180 s for the remainder. See text.

† Electronic supplementary information (ESI) available: summary of kinetic results for reaction of **1** with EtONa. See http://www.rsc.org/suppdata/cc/b0/b006439o/

DOI: 10.1039/b006439o

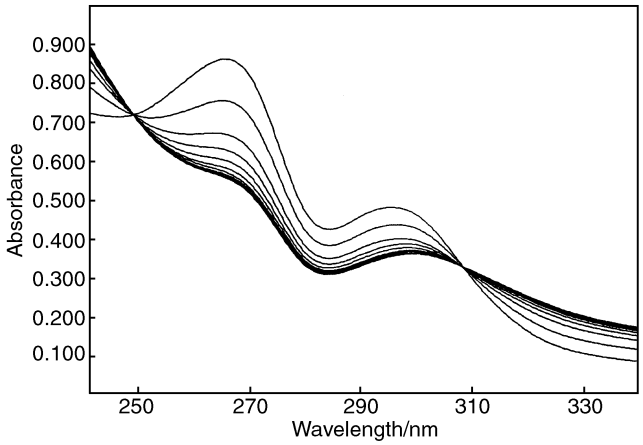


Fig. 2 Repetitive scanning of the stopped-flow spectra for the reaction of **1** with EtONa (**1** ⇌ **2**) in anhydrous EtOH at 25.0 ± 0.1 °C. [**1**] = 8.12×10^{-5} M, [EtONa] = 13.0×10^{-3} M. Time interval = 2 ms.

the fast equilibrium process (**1** ⇌ **2**) can be calculated according to eqn. (1), *i.e*. from the slope and intercept of the plot of k_{obs} *vs*. [EtONa]. The k_1 and k_{-1} values determined in this way are 14,500 $M^{-1}s^{-1}$ and 30.5 s^{-1}, respectively.

$$k_{obs} = k_1[\text{EtONa}] + k_{-1} \quad (1)$$

In order to determine the k_2 value in Scheme 1, the slow reaction process (**1** ⇌ **2** → **3**) has been monitored. The plot of k_{obs} *vs*. [EtONa] yields a curvilinear trace that levels off as the concentration of EtONa increases (Table 2, ESI†). Eqn. (2) may be derived for a reaction which proceeds through a rapid pre-equilibrium as in the present system.[13]

$$k_{obs} = k_1k_2\,[\text{EtONa}]/\{k_1[\text{EtONa}] + k_{-1} + k_2\} \quad (2)$$

Eqn. (2) resembles the Michaelis–Menten equation[14] which accounts for enzyme catalyzed reactions. In this case, the plot of k_{obs} *vs*. [EtONa] should reach a maximum and then flatten out as the concentration of EtONa increases, as found in the present system. Rearrangement of eqn. (2) gives eqn. (3).

$$1/k_{obs} = 1/k_2 + \{k_{-1} + k_2\}/\{k_1k_2\,[\text{EtONa}]\} \quad (3)$$

Consequently, if the present reaction proceeds as in Scheme 1, the plot of $1/k_{obs}$ *vs*. 1/[EtONa] should be linear. In fact, a linear plot has been obtained (Fig. S1, ESI†). From the intercept of the linear plot, the $1/k_2$ value has been calculated. The k_2 value determined in this way is 1.36×10^{-3} s^{-1}, which is much smaller than the k_{-1} value. The relative magnitude of these microscopic rate constants is clearly consistent with the preceeding proposal based on the spectral data shown in Figs. 1 and 2. The small k_2 (1.36×10^{-3} s^{-1}) as compared to k_{-1} (30.5 s^{-1}) would permit observation of the putative intermediate **2**.

Since ethoxide is more basic than aryloxide by 4–5 pK_a units in EtOH,[6b] one might expect EtO^- would be a poorer leaving group than aryloxide. However, in fact, the k_{-1} value has been determined to be over 10^4 times larger than the k_2 value in the present system. Therefore, the present result is quite surprising, and suggests that basicity alone does not determine nucleofugality in this system. Since cyclic sulfinate esters have been suggested to be thermodynamically stable,[15–17] one might suggest that thermodynamic stability of **1** would accelerate the k_{-1} step and retard the k_2 step in Scheme 1. This argument gains support from the fact that the product (**3**) reverts quantitatively to the reactant (**1**) upon acidification of the reaction mixture. However, solvent effect may also be important in the present system. Note that reaction of **1** with OH^- in H_2O is much faster than the corresponding reaction with EtONa in EtOH,[7a] and there is no accumulation of intermediate in H_2O (Fig. S2, ESI†, *e.g*. good isosbestic points at 242 and 306 nm). Furthermore, we have noticed that the reaction of **1** with EtONa is accelerated significantly by addition of H_2O into the reaction medium, even in very small amounts.

However, more systematic studies are required in order to elucidate how the solvent stabilizes or destabilizes reactants, TS and intermediate. Reactions of **1** with various nucleophiles and in different solvents are currently under way to investigate further the reaction mechanism.

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