# Evidence for an Isocyanate Formation in the Alkaline Hydrolysis of $N^1$-Alkyl Derivatives of Chlorpropamide, Inhibitors of Aldehyde Dehydrogenase

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Trapping of a propyl isocyanate intermediate and entropies of activation data are consistent with an elimination–addition mechanism $A_{xh}D_H + D_N$ (E1cB) for the hydrolysis of 1-alkyl-1-[(4-chlorophenyl)sulfonyl]-3-*n*-propylurea, the $N^1$-alkyl derivatives of chlorpropamide, inhibitors of aldehyde dehydrogenase.

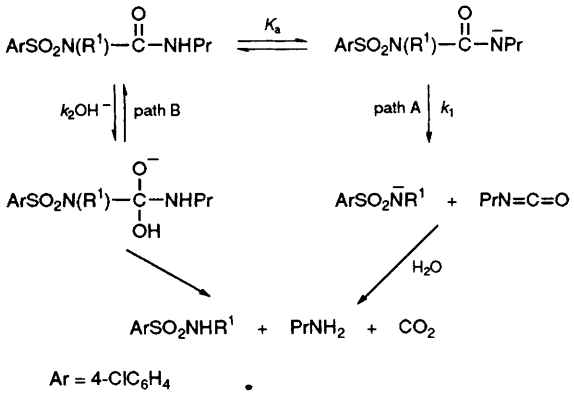


Acyl[1] and sulfonyl[2] group transfers, in particular, those involving elimination–addition reaction intermediates, such as ketenes[3,4] and isocyanates[5,6] for the former, or sulfene[7] for the latter, have been thoroughly studied. The mechanism of decomposition of *N*-methyl-*N*-nitrosoureas[8] and that of their intermediates, *i.e.* methanediazoates,[9] have been elucidated recently. However, there are no fundamental studies on the reactivity in aqueous media of sulfonylureas $ArSO_2NHCONHR$ despite their wide applications in medicinal[10] and agrochemical[11] fields. Recently, Nagasawa and co-workers[12] have observed that only $N^1$-alkyl-substituted derivatives of chlorpropamide (Ar = 4-$ClC_6H_4$, R = $Pr^n$), able to release alkyl isocyanate, are inhibitors of aldehyde dehydrogenase (AlDH) while the analogous carbamates are inactive. However, these authors put forward this hypothesis without proving the formation of this electrophilic intermediate which would react with a cystein sulfhydryl group at the active site of the enzyme.

*N*-Arylureas are not very labile because the electrophilicity of the carbonyl group is considerably weakened by the donor effects of the lone pairs on the two nitrogen atoms. However, their hydrolyses have been carried out in strongly basic and acidic conditions at 100 °C and an A1 mechanism has been proposed with water playing the role of a proton transfer agent.[13]

Sulfonylureas with a strong electron-withdrawing group enhancing the electrophilic character of the reactive site are expected to be more reactive. However, these compounds with $pK_a$ values lying between 3 and 7 are fully ionized in alkaline media and posses poor $RNH^-$ leaving groups. They are therefore less reactive than expected as shown by the results obtained for $N^3$-derivatives of 4-tolylsulfonylureas.[14]

When these sulfonylureas are $N^1$-substituted by alkyl and aryl groups, they are weakly ionizable ($pK_{aN^3H} > 14$) and we found that they are easily hydrolysed in alkaline media. We report here our preliminary results of a study of the alkaline hydrolysis of $N^1$-alkyl derivatives of chlorpropamide **1a–e** involving acyl group transfer through an elimination–addition mechanism, $A_{xh}D_H + D_N$(E1cB).




**Scheme 1**

*N*-Propyl-4-chlorobenzenesulfonamide was characterized as the product of alkaline hydrolysis of **1b** by comparison of the UV spectrum of the final mixture (0.01 mol $dm^{-3}$ NaOH, 25 °C) with that of an authentic sample of this sulfonamide recorded under the same experimental conditions. This result suggests that the hydrolysis of compounds **1a–e** occurs by acyl group transfer as depicted in Scheme 1.

Two major types of reaction mechanisms can be envisaged for acyl group transfer: (i) an elimination–addition mechanism (path A), $A_{xh}D_H + D_N$(E1cB); (ii) an addition–elimination pathway (path B), $A_N + D_N(B_{Ac}2)$. Path A involves deprotonation of the nitrogen atom to form an anion which decomposes in a monomolecular rate-determining step into propyl isocyanate and *N*-alkyl-4-chlorobenzenesulfonamide anion. This propyl isocyanate intermediate then reacts rapidly with water or hydroxide ion to give propylcarbamic acid which decarboxylates to propylamine and carbon dioxide. In path B the rate determining nucleophilic attack of hydroxide ion on the carbonyl takes place to give a tetrahedral intermediate which decomposes to the final products.

The hydrolysis of **1a–e** in alkaline media at 25 °C obeyed excellent pseudo-first-order kinetics up to at least 90% of reaction. In aqueous buffered solutions, the reaction rates were found to be independent of the nature and concentration of buffer (borax, carbonate, triethylamine, piperidine). In the studied region where $a_H \gg K_a$, the rate constants measured spectrophotometrically for **1c** vary proportionally with pH and are in agreement with the rate laws $k_{obs} = k_1K_a/(K_a + a_H)$ for path A and $k_{obs} = k_2K_w/(K_a + a_H)$ for path B. The plateau region where $k_{obs}$ would be independent of pH cannot be obtained owing to the high $pK_a$ value of $N^3H$ group ($pK_a \approx 18$ for the *N*-methylurea). Bimolecular rate constants $k_{OH}$ are reported in Table 1.

Distinction between these two mechanisms was made using the following criteria. For all sulfonylureas, the entropies of activation were calculated from measurements of $k_{obs}$ in 0.01 mol $dm^{-3}$ NaOH solutions, where $k_{OH}$ is composite and equal to $k_1K_a/K_w$ or $k_2$, at five temperatures from 15 to 35 °C and the values were found to be positive or slightly negative (see Table 1). These results are in favour of a dissociative process rather than an associative one for which the expected values of the entropies of activation would be strongly negative and lie generally between −80 and −170 J $mol^{-1}$ $K^{-1}$ for esters[15] and *N*,*N*-disubstituted carbamates.[16] Although added piperidine had no effect on the rate

**Table 1** Bimolecular rate constants $k_{OH}$, entropies and enthalpies of activation values for the hydrolysis of 4-$ClC_6H_4SO_2N(R^1)CONHPr^n$ at 25 °C (μ = 1.0, KCl)

| Cmpd. | $R^1$ | $k_{OH}$/ $10^{-1}$ $dm^3$ $mol^{-1}$ $s^{-1}$ | $\Delta S^{\ddagger}$/ J $mol^{-1}$ $K^{-1}$ | $\Delta H^{\ddagger}$/ kJ $mol^{-1}$ |
|---|---|---|---|---|
| **1a** | Me | 2.7 ± 0.1 | 31.3 ± 8.4 | 97.4 ± 2.4 |
| **1b** | $Pr^n$ | 3.6 ± 1 | 36.0 ± 9.6 | 68.4 ± 1.8 |
| **1c** | $Pr^i$ | 21.1 ± 1 | −47.6 ± 5.8 | 97.8 ± 2.9 |
| **1d** | $Bu^n$ | 4.2 ± 0.2 | −16.7 ± 6.2 | 82.2 ± 1.9 |
| **1e** | Bn | 7.6 ± 0.6 | 11.7 ± 0.8 | 89.1 ± 0.3 |

of 4-chlorobenzenesulfonamide release from **1a**, product analysis using $^{13}C$ NMR indicated that in the presence of piperidine, the sulfonylurea **1a** was entirely converted to *N*-(propylcarbamoyl)piperidine.† The NMR spectrum of the final products was found to be identical with that of an equimolecular mixture of this urea and *N*-methyl-4-chlorobenzenesulfonamide. These data are consistent with attack of piperidine on an intermediate propyl isocyanate after sulfonamide liberation.

From our results, in particular the trapping experiment, it can be concluded that the hydrolysis of this series of sulfonylureas occurs by an $A_{xh}D_H + D_N$ mechanism with formation of propyl isocyanate and this may account for their inhibition properties against aldehyde dehydrogenase.

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† Trapping experiment: 1-methyl-1-(4-chlorophenyl)sulfonyl-3-n-propylurea **1a** (580 mg, 2 mmol) dissolved in dioxan (10 $cm^3$) was added to a solution of piperidine (200 $cm^3$, 0.5 mol $dm^{-3}$ total buffer concentration, fraction base = 0.5, ionic strength 1.0 mol $dm^{-3}$, KCl). The reaction mixture was stirred overnight at 25 °C then acidified with 3 mol $dm^{-3}$ HCl. The aqueous phase was extracted with dichloromethane and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and gave a residue identified as a mixture of *N*-methyl-4-chlorobenzenesulfonamide and *N*-(propylcarbamoyl)-piperidine.

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