The hydrolytic reactivities of *N*-methyl-*N*-(methylthiomethyl)acetamide and *N*-acetyl-1,3-thiazolidine: the influence of the sulfur atom

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Sosale Chandrasekhar* and S. Srinivasa Gopalan

Department of Organic Chemistry, Indian Institute of Science, Bangalore 560 012, India

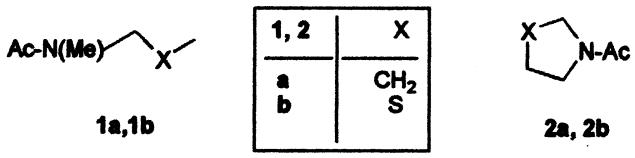
The sulfur atom in the substrates leads to modest enhancements in the titled phenomena: these are essentially derived from favourable enthalpies of activation, the negative entropies of activation possibly indicating a measure of stereoelectronic control.

Keywords: sulfur atom, *N*-methyl-*N*-(methylthiomethyl) acetamide, *N*-acetyl-1,3-thiazolidine

The carboxylic amide group is of paramount importance in biological systems such as the proteins and the β-lactam antibiotics, so substituent effects on their reactivity are of much interest. In the present study, the effect of an *N*-methylthio moiety on amide hydrolysis was addressed, particularly as this moiety is present in several of the β-lactam antibiotics.[1,2]

The systems studied were the *N*-(thiomethyl)amides **1b** and **2b**, and their corresponding dethia analogues **1a** and **2a** (Scheme 1); **1b** was prepared by alkylating *N*-methylacetamide with chloromethyl methyl sulphide (*via* NaH deprotonation in THF);[3] **2b** and the dethia analogs **1a** and **2a** were prepared by standard methods. The kinetics of the basic hydrolysis of these derivatives in 0.4 M aqueous NaOH were determined spectrophotometrically, by following their disappearance in the 205 nm region as reported for *N*,*N*-dimethylacetamide.[5a] Activation parameters were obtained by determining the second order rate constants at three different temperatures in the case of **1b** and **2b.** The kinetic data are collected in Table 1.

These clearly show that the sulfur atom in both **1b** and **2b** enhances the reactivity of the *N*-acyl group towards basic cleavage–by a factor of 3.7 in the acyclic case **1,** and a factor of 9.8 in the cyclic case **2.** Electron withdrawal by the sulfur atom appears to be the simplest explanation for the enhanced reactivities of **1b** and **2b.** The high negative entropies of activation in the case of both **1b** and **2b** indicate highly ordered transition states, which may well derive from a stereoelectronic alignment of the *C*–*S* bond periplanar to the amide π system. (Such stereoelectronic control is known in the analogous but reverse process of nucleophilic addition to iminium ions.[8]) The higher reactivity in both the cyclic cases **2** relative to their acyclic counterparts **1** is attributed to release of ground state strain. This is supported by the more favourable enthalpy of activation in the case of the thiazolidine **2b** relative to the acyclic analog **1b** (by at least 4.3 kcal/mol), although a large part of this is offset by an unfavourable entropy of activation.



Scheme 1

Table 1 Second order rate constants and activation parameters for the basic hydrolysis of the amide derivatives **1** and **2**, in 0.4 M NaOH at 64°C[a]

Substrate	$10^4 k_2$ M^{-1} s^{-1}	$\Delta H^{\ddagger}$ kcal/mol	$\Delta S^{\ddagger}$ e.u.	$\Delta G^{\ddagger}$ kcal/mol
1a	0.30 ± 0.02			
1b	1.10 ± 0.02	15.2 ± 0.95	–31.6 ± 2.9	25.9 ± 1.9
2a	1.07 ± 0.02			
2b	10.50 ± 0.75	8.6 ± 1.4	–46.9 ± 4.3	24.4 ± 2.8

[a]Rates determined also at 72°C and 80°C (in the case of **1b**), and 44°C and 54°C (in the case of **2b**); kinetic runs repeated at least thrice; *r* always > 0.9.

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* To receive any correspondence. E-mail: sosale@orgchem.iisc.ernet.in