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Phthalimidomethyl as a Drug Pro-moiety. Probing its Reactivity

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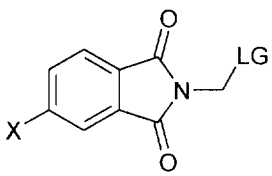
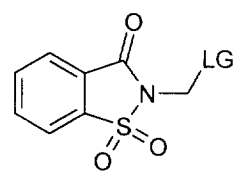
Abstract: Phthalimidomethyl derivatives **1**, encompassing a wide range of leaving group abilities, are rapidly hydrolysed to the corresponding phthalamic acid *via* rate-determining attack at the phthalimide carbonyl group.

Compounds containing the phthalimidomethyl moeity, e.g. **1**, are of interest in drug chemistry because of their potential as labile prodrugs. For the hydrolysis of **1**(LG = OAr) and the saccharin derivatives **2** (LG = OAr), an S_N2 mechanism involving rate-limiting attack of HO^- at the methylene bridge has been reported [1]. In both cases, it was suggested that phenol was the leaving group, despite the pK_as of phthalimide and saccharin being *ca.* 1.7 and 8.4 units lower, respectively, than that of phenol [1]. Recently, compounds **2** (LG = OAr, SAr, OCOAr and Cl) were reported to be potent human leukocyte elastase (HLE) inhibitors[2]. The proposed mechanism of HLE inhibition involves nucleophilic attack of a serine residue at the carbonyl group of the saccharin moiety[2a,b], though the evidence for this is ambiguous. We now report a study [3] of the alkaline hydrolysis of phthalimidomethyl compounds **1**, encompassing a wide range of potential leaving group abilities Cl^-, ONO_2^- [4], OCOR [5], MeO^- [6] and H^- [7] (Table 1), which reveals that compounds **1** react with HO^- preferentially at the phthalimide carbonyl carbon atom.



1



2

Products. The major product of alkaline hydrolysis of **1** is the phthalamic acid, **6**, (Scheme) except for **1k**, which forms *N*-methylphthalamic acid. *N*-Hydroxymethylphthalimide was not detected in any reaction. Small amounts (*ca.* 5%) of phthalimide, which may arise from *N*-hydroxymethylphthalimide, were detected. Benzylpenicillin was recovered quantitatively from **1c**; thus the β-lactam ring is less reactive than the phthalimide moiety.

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Table 1. Second-order rate constants, k_{HO^-}, for the alkaline hydrolysis of compounds 1 at 37 °C.

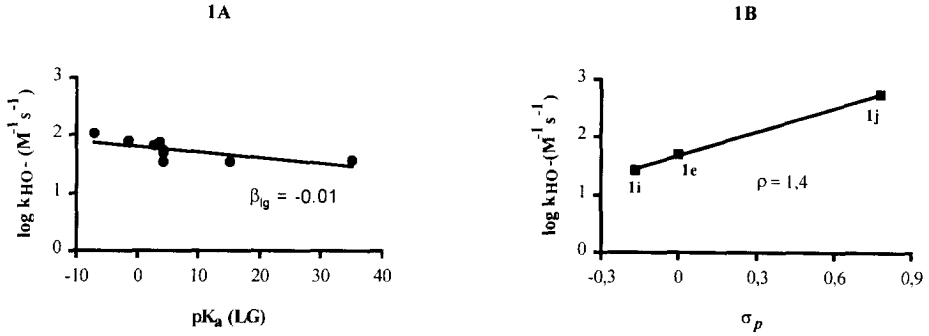
Compound	X	LG	m.p./°C	$k_{HO^-}/M^{-1}s^{-1}$
1a	H	Cl	*a*	105.8
1b	H	ONO_2	79-82	79.7
1c	H	benzylpenicilloate	*b*	65.6
1d	H	$OCOC_6H_4$-4-MeO	125-7	33.9
1e	H	$OCOC_6H_5$	105-6	50.4
1f	H	$OCOC_6H_4$-4-Cl	170-2	56.7
1g	H	$OCOC_6H_4$-4-NO_2	197-9	76.8
1h	H	OMe	113-5	35.3
1I	4-Me	$OCOC_6H_5$	115-8	27.3
1j	4-NO_2	$OCOC_6H_5$	134-5	559.0
1k	H	H	*a*	37.5

a) From Aldrich Chemical Co.; b) hygroscopic gum

Kinetics and mechanism. The hydrolysis of **1** is accompanied by absorbance decreases at 230nm (large) and 300nm (small), both ascribed to phthalimide ring opening [8]. Phthalimide behaves similarly, but at rates that are 10-100 fold slower than **1** (data not shown), while *N*-hydroxymethylphthalimide decomposes instantaneously to phthalimide under the experimental conditions. The second-order rate constants, k_{HO^-}, (Table 1)[9] are characterised by:

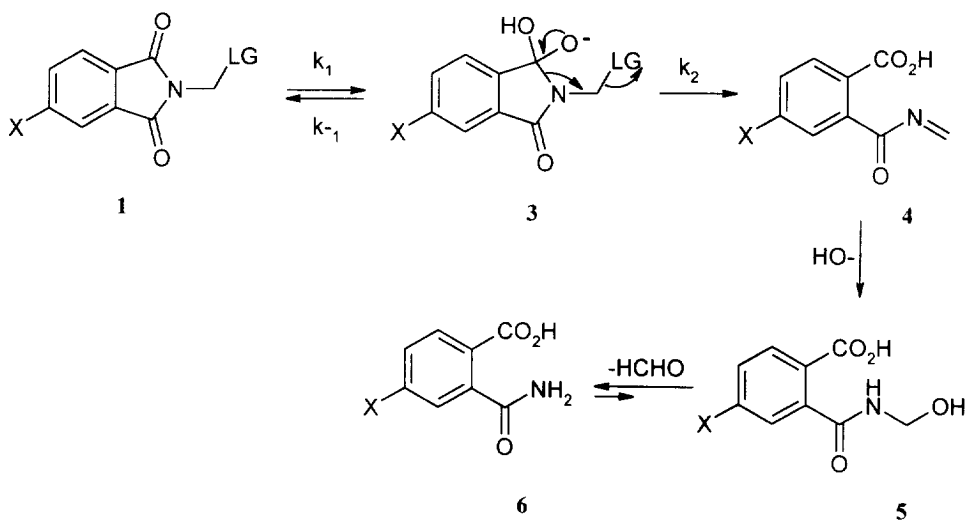
- a negligible dependence on leaving group ability (β_{lg} = -0.01) (Figure 1A) [10], and
- a high susceptibility to the substituent in the phthalimide moiety (ρ = 1.4) (Figure 1B).

Figure 1. Dependence of the second-order rate constants, k_{HO^-}, for compounds 1 upon A: the pK_a of the leaving group, and B: the substituent in the phthalimide moiety.



These results, together with the observation that *N*-methylphthalimide, **1k**, (which lacks a leaving group on the methylene carbon atom) is only 3-fold less reactive than **1a**, are inconsistent with an S_N2 attack of HO^- at the methylene bridge. This would yield phthalimide (*via* *N*-hydroxymethylphthalimide), yet phthalimide hydrolyses at substantially slower rates than those observed for **1**. For the S_N2 mechanism, a substantially higher dependence of log k_{HO^-} on the pK_a of the leaving group should be observed,[11] while only a small dependence upon the substituent in the phthalimide ring would be expected. Consequently, we propose that alkaline hydrolysis of **1** involves rate-limiting formation of a tetrahedral intermediate **3**, which decomposes to **6** *via* intermediates **4** and **5** (Scheme). We did not observe any peak in the HPLC that could be ascribed to **5**, though loss of formaldehyde from **5** would be expected to be slow, [12] especially at the lower pH values. However, our attempts to synthesise **5** failed, which may indicate that the *ortho*-CO_2^- group acts as a general base catalyst for the loss of formaldehyde from **5**, similar to its function in the hydrolysis of *o*-carboxyphthalimide. [13]

Scheme



In conclusion, phthalimidomethyl compounds **1** have high intrinsic reactivity, and contrary to previous reports, react with nucleophiles preferentially at the carbonyl carbon of the phthalimide ring. This, suggests that, as analogues of **2**, compounds **1** may be attractive candidates as HLE inhibitors. Indeed, the closely related acyloxymethylsuccinimides are reported to inhibit HLE. [14]

References and Notes

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3. Hydrolyses in pH 9.4-11.6 aqueous solutions containing 20% (v/v) acetonitrile were monitored by UV. First-order rate constants, k_{obs}, were determined from plots of $\ln(A_t-A_\infty)$ *vs.* time. Second-order rate constants, k_{HO^-}, were determined from plots of k_{obs} *vs.* $[HO^-]$. Products were identified and quantified by HPLC: Merck LiChrospher RP-8 5μm column; 15% acetonitrile - aqueous $5x10^{-3}$ M $Bu_4NH_2PO_4$ (pH 5.90) eluant; retention times at a flow rate of 1ml/min: **6**, 3.8 min; *N*-hydroxymethylphthalimide, 5.7 min; phthalimide, 7.5 min.
4. Synthesis of **1b**: *N*-hydroxymethylphthalimide (2 mmol) was added slowly to conc. HNO_3 (20 ml) at 0 °C. After 30 min, the reaction mixture was poured over ice-water and the precipitate filtered to yield **1b** (53%). δ_H: 5.97 (2H, s, NCH_2O), 7.65-7.97 (4H, m). Found (calc.) C, 48.5 (48.6); H, 2.71(2.70); N, 12.4 (12.6)%.
5. Esters **1c** (Jansen, A.B.A.; Russel, T.J.; *J.Chem.Soc.*, **1965**, 2127) and **1d-g** and **1i,j** (Iley, J.; Moreira, R.; Rosa, E.; *J.Chem.Soc. Perkin 2*; **1991**, 563) gave satisfactory elemental analyses and spectral data
6. Compound **1h** was prepared in 21% yield from *N*-hydroxymethylphthalimide (2.5 mmol) and absolute methanol (10 ml) using conc. H_2SO_4 (0.5 ml) as catalyst. δ_H: 3.42 (3H, s, CH_3O), 5.05 (2H, s, NCH_2O), 7.78-7.82 (4H, m). Found (calc.) C, 62.3 (62.8); H, 4.67 (4.71); N, 7.10 (7.33)%.
7. $pK_a = 35$ (Buncel, E; Menon, B; *J. Am. Chem. Soc.*, **1977**, *99*, 4457).
8. See Khan, M.N. *J. Chem. Soc.*, **1988**, 1129 and Khan, M.N. *J. Org. Chem.*, **1996**, *61*, 8063.
9. The k_{HO^-} values contain contributions from the reactions leading to phthalamic acid and phthalimide. However, the amounts of phthalimide are small, independent of the leaving group and don't vary with $[HO^-]$.
10. The smaller set of esters **1d-g** yields a ρ of 0.28 ($n = 4$, $r^2 = 0.836$). This is considerably smaller than the ρ of 2.55 for the alkaline hydrolysis of ethyl benzoates. See reference 11, pp. 145.
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