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# Phthalimidomethyl as a Drug Pro-moiety. Probing its Reactivity

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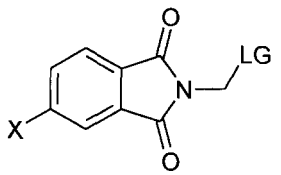
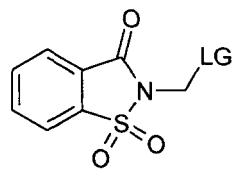
**Abstract:** Phthalimidomethyl derivatives **1**, encompassing a wide range of leaving group abilities, are rapidly hydrolysed to the corresponding phthalamic acid *via* rate-determining attack at the phthalimide carbonyl group.


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 $pK_a$s 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.**

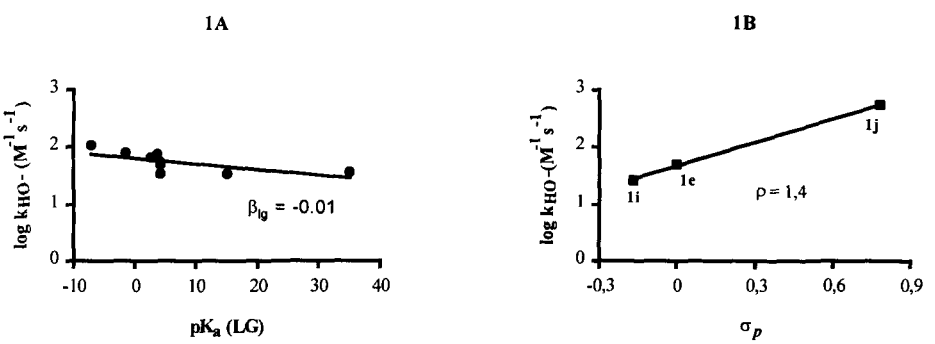
| Compound | X | LG | m.p./°C | $k_{HO^-}/M^{-1}s^{-1}$ |
|---|---|---|---|---|
| **1a** | H | Cl | *a* | 105.8 |
| **1b** | H | $ONO_2$ | 79-82 | 79.7 |
| **1c** | H | benzylpenicilloate | *b* | 65.6 |
| **1d** | H | $OCOC_6H_4$-4-MeO | 125-7 | 33.9 |
| **1e** | H | $OCOC_6H_5$ | 105-6 | 50.4 |
| **1f** | 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:

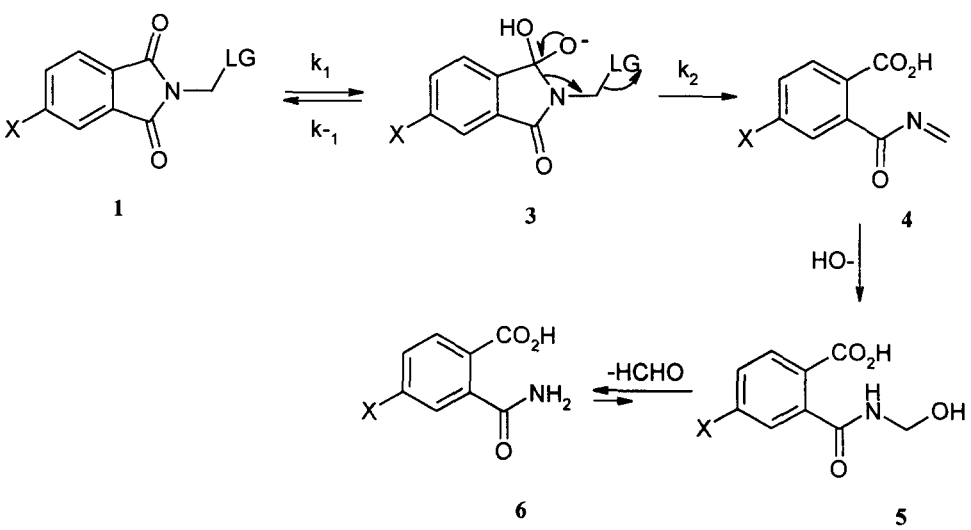
- a negligible dependence on leaving group ability ($\beta_{lg}$ = -0.01) (Figure 1A) [10], and
- a high susceptibility to the substituent in the phthalimide moiety ($\rho$ = 1.4) (Figure 1B).

**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**




**1** **3** **4** **6** **5**

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%). $\delta_H$: 5.97 (2H, s, NC*H*$_2$O), 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. $\delta_H$: 3.42 (3H, s, C*H*$_3$O), 5.05 (2H, s, NC*H*$_2$O), 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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