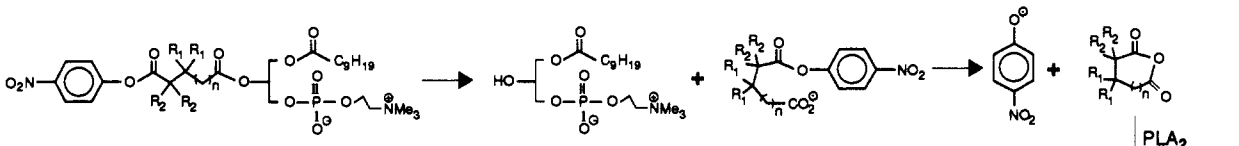
Scheme I



1a n=1; R_1, R_2 = H
1b n=1; R_1=H, R_2 = Me
1c n=1; R_1 = Me, R_2 = H
1d n=0; R_1, R_2 = H
1e n=0; R_1 = H, R_2 = Me

2a n=1; R_1, R_2 = H
2b n=1; R_1=H, R_2 = Me
2c n=1; R_1 = Me, R_2 = H
2d n=0; R_1, R_2 = H
2e n=0; R_1 = H, R_2 = Me

Table I. Efficiency of Hydrolysis and Inhibition

substrate	V, μmol min^{-1} mg^{-1}	P[a]	release fragment	$t_{1/2}$ cyclization,[b] s
1a	155[c]		**2a**	150
1b	0.11	19	**2b**	40
1c	0.002	9	**2c**	15
1d	0.6	35	**2d**	4
1e	0.005	11	**2e**	1
			2f[d]	30

[a] Partition ratio (P) expressed as moles of dye released per mole of enzyme inactivated. [b] The rate constants for cyclization of *p*-nitrophenyl esters **2a** and **2f**[15] were measured spectrophotometrically at pH 8 at 20 °C and found to be 700 times faster than the literature values[16] for the corresponding phenyl esters. The $t_{1/2}$'s for **2b–e** were calculated from the literature values for the corresponding phenyl esters,[16] assuming that the *p*-nitrophenyl ester cyclized 700 times faster. [c] Taken from ref 9. [d] **2f** is *p*-nitrophenyl 3,3-dimethylglutarate.[15]

cubation of PLA_2 with **1b** or **1d** had little effect on the rate of inactivation, but did increase P. Presumably, higher temperatures favor diffusion of the hydrolysis products **2** away from the enzyme, thereby resulting in the cyclic anhydride being generated in bulk solution. The dimethylglutarates **1b** and **1c** and the dimethylsuccinate **1e** are more efficient suicide inhibitors than **1d**; on average, the enzyme processes 10–20 substrates before being inactivated. Inhibitor **1d** is the best substrate but the least efficient of the inhibitors despite the fact that **2d** cyclizes faster than **2b** or **2c**. Presumably, hydrophobic geminal methyl groups also enhance the association of **2** to the enzyme. The overall rate of inactivation is a reflection of not only susceptibility of **1** to enzymatic hydrolysis and the rate of intramolecular cyclization of **2** but also the rate of diffusion of **2** from the enzyme.

The effect of inhibitor concentration is shown in Figure 2 for succinate **1d**. Inhibition of a 70 nM solution of PLA_2 is quite rapid even at 1.7 μM inhibitor. The 10% inactivation observed for 0.5 μM **1d** was consistent with P = 35 since a 7:1 ratio of **1d**/PLA_2 meant **1d** would be consumed before complete PLA_2 inactivation. Inhibition was observed even at lower concentrations provided the ratio of inhibitor/PLA_2 exceeded 40, indicating that the binding affinity for these inhibitors is high.

Inhibition of other PLA_2 enzymes was also observed. We are further investigating the mechanism by which these exceedingly potent, efficient, and selective inhibitors of PLA_2 function.

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Computer Software Reviews

MacFormula. Version 2.0. By James E. Deline, Ph.D., 3857 MacGregor Commons, Livermore, CA 94550. List price $15.00 plus a blank disk for the desk accessory version; standalone version is shareware.

MacFormula is a program for the Apple Macintosh that is designed to calculate the average molecular weight, the "exact mass" molecular weight, and the elemental analysis (of up to 20 constituent atoms) for any molecular formula entered by the user. In these aspects, MacFormula is identical with the Apple Chemintosh molecular mass calculator, a freeware desk accessory which is the only other program of this type known to this reviewer. However, MacFormula possesses two unique additional features that make it worth the very modest purchase price. One of these is MacFormula's ability to calculate the number of millimoles that corresponds to an entered number of milligrams (of the already entered molecular formula), or vice versa (millimoles to milligrams). This is an extremely common calculation for most chemists. The second unique feature of MacFormula is its ability to utilize user-defined symbols to represent the masses of molecular subunits. Thus if a chemist is working with a series of molecules that all bear the same subunit, for example a phenyl substituent, then he or she can calculate the mass of that subunit, then create a unique, stored symbol (e.g. "Ph") having that mass. This obviates the need for the chemist to determine the molecular formula of each molecule in the series according to all of the atoms contained, a task that can be quite tedious when large molecules are involved.

MacFormula is extremely easy to learn and to use and will be very useful in industrial and academic laboratories and offices. In order to keep the price of MacFormula so low, the program's author requests users to send him a blank disk with their payment. In return, users become registered to receive updated versions, and they receive copies of the standalone version, which is shareware, and the desk accessory version, which is not shareware nor in the public domain.

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