from the clinical trial are intended for designing a rational dosage regimen. The mean volume of distribution calculated from the test subjects should accurately predict their own plasma levels, even if the information is not intended for designing a rational dosage regimen.

In some studies, all individual plasma or serum data from the test subjects were grouped together and the pharmacokinetic analysis was performed based on these arithmetical *averaged* plasma or serum data (9). In intravenous bolus studies, the calculated mean initial volume of distribution obviously will be identical to the value calculated by the harmonic mean method and different from that calculated by the arithmetic mean method. This fact, which has probably not been pointed out before, might contribute to the difference in values reported from different studies.

In an earlier study (10) on clinical theophylline pharmacokinetics, the investigators reported that, depending on the methods used to calculate the mean total body clearance, as much as a 25–30% difference in the recommended infusion rate could occur. This phenomenon was considered as "unfortunate" (10). This author has made a similar analysis as presented in this communication and concluded that the best method for calculating the mean total body clearance in designing a rational dosage regimen is the harmonic mean method. Details of analyses will be reported later.

The preceding discussion is based on the assumption that the arithmetic mean method be used for the calculation of the mean plasma level. This approach was justified because the arithmetic mean method has been used almost exclusively for averaging peak, trough, steady-state, or mean steady-state plasma levels of drugs or metabolites in pharmacokinetic studies. This is probably also the case with mean levels of endogenous substances such as creatinine and urea reported in the literature. Statistically speaking, if the geometric, harmonic, or other mean method can be shown to be the best method for averaging plasma level data, then a different conclusion regarding the proper method for averaging the apparent volume of distribution can be obtained. The method proposed here can be applied to the calculation of other mean volumes of distribution such as the distribution volume at steady state.

In estimating the apparent volume of distribution of drugs after oral administration, the potential hepatic and pulmonary first-pass effects are often ignored. Appropriate equations are available for correcting for such effects (11–13). The harmonic mean method has been recommended for the calculation of the mean biological half-life of drugs (14).

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Prostaglandin Prodrugs IV: Empirical Relationship between Functional Group Contributions and Melting Points of C_1-Esters

Keyphrases □ Prostaglandins—influence of functional group on melting points, dinoprostone and dinoprost C_1-esters □ Prodrugs—prostaglandins, influence of functional group on melting points, dinoprostone and dinoprost C_1-esters □ Dinoprost and dinoprostone C_1-esters—influence of functional group on melting points

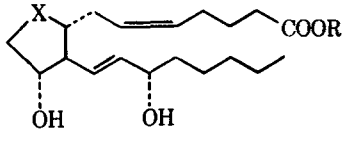
To the Editor:

Many prostaglandins occur as viscous liquids at room temperature, which presents problems in various pharmaceutical processes such as weighing and formulation. We recently showed that certain crystalline esters of the E-series prostaglandins are remarkably more stable than the parent prostaglandins (1). Now, based on melting-point data of numerous dinoprostone (I) and dinoprost (II) C_1-esters accumulated in our laboratories, we present a functional group contribution analysis of the influence of structure on melting points.

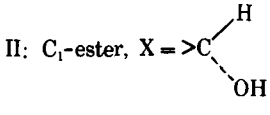
In principle, the melting point (T_m) of a substance can be calculated from:

$$T_m = \frac{\Delta H_f}{\Delta S_f} \qquad \text{(Eq. 1)}$$

where ΔH_f and ΔS_f are the heat and the entropy of fusion,



I: C_1-ester, X = >C=O



II: C_1-ester, X = >C

Table I—Group Contribution Values to Heat of Sublimation [a]

Group	$\Delta H_s°$, kcal/mole	Group	$\Delta H_s°$, kcal/mole
$-CH_3$	2.45	—O—, aliphatic	1.55
$-C_2H_5$	4.28	—O—, aromatic	1.0
$-CH_2-$	2.0	—OH, aliphatic	8.2
$=CH-$	2.0	—OH, aromatic	6.8
Phenyl	$8.4 + \frac{1.6^b}{N}$	>C=O, aliphatic	5.6
Naphthyl	15.0	>C=O, aromatic	3.6
$-NH_2$ (aliphatic)	6.35	>C=O, hetero-aromatic	6.0
$-NH_2$ (aromatic)	6.5	—F, aromatic	1.9
—NH (aliphatic)	4.5	—O—C(=O), aliphatic	4.4
—NH (aromatic)	6.5[c]	—Br, aliphatic	3.34
$-NO_2$ (aliphatic)	9.6	—Br, aromatic	4.28
$-NO_2$ (aromatic)	6.8	—I, aromatic	5.03

[a] See Ref. 2 for more extensive data. [b] Number of carbon atoms in the ring substituents. [c] Approximated value.

respectively. When a given substance undergoes an isothermal process, thermodynamic parameters associated with the process such as ΔH_f and ΔS_f can be approximated as the sum of the contributions of each functional group present in the molecule. For an ester, we would like to consider the values of ΔH_f and ΔS_f as the sum of the contributions by the prostaglandin (PG) and the ester alkyl or aryl (R) moieties. Thus, Eq. 1 becomes:

$$T_m = \frac{\Delta H_f^{PG} + \Delta H_f^{R}}{\Delta S_f^{PG} + \Delta S_f^{R}} \qquad \text{(Eq. 2)}$$

The prostaglandin group contribution should be constant for a series of prostaglandin C_1-esters, whereas the R group contribution varies depending on the structure. This group contribution approach appears to be quite valid for a series of dinoprostone C_1-phenyl esters in which the melting points are well correlated with those of the parent phenols (1).

In the present analysis, instead of handling both the heat and the entropy contributions, we are making a key assumption that the overall entropy of fusion is constant for the following two reasons. First, the group entropy contribution of the prostaglandin group is expected to predominate, mainly because the molecular size of these esters is largely determined by the prostaglandin group rather than the R group. The molecular weights of the esters are rather constant (570 ± 100). In this context, the entropy of fusion is considered to consist of two components: that due to the volume change and that due to the true entropy change upon fusion at constant volume (2). Thus:

$$\Delta S_f^{PG} + \Delta S_s^{R} \cong \Delta S_f^{PG} = \text{constant} \qquad \text{(Eq. 3)}$$

Second, we can approximate ΔS_f^{PG} to be constant if ΔS_f^{R} cannot be neglected with respect to ΔS_f^{PG}:

$$\Delta S_f^{R} = \Delta S_s^{R} - \Delta S_v^{R} \qquad \text{(Eq. 4)}$$

where ΔS_s^{R} and ΔS_v^{R} are the entropies of sublimation and vaporization, respectively. The entropy of sublimation is relatively constant for organic compounds of moderately constant size. For example, of 136 compounds for which ΔS_s values were compiled (3), over 100 compounds showed ΔS_s values within 50 ± 15 eu. As expected, extreme deviations are reported when the compounds become very

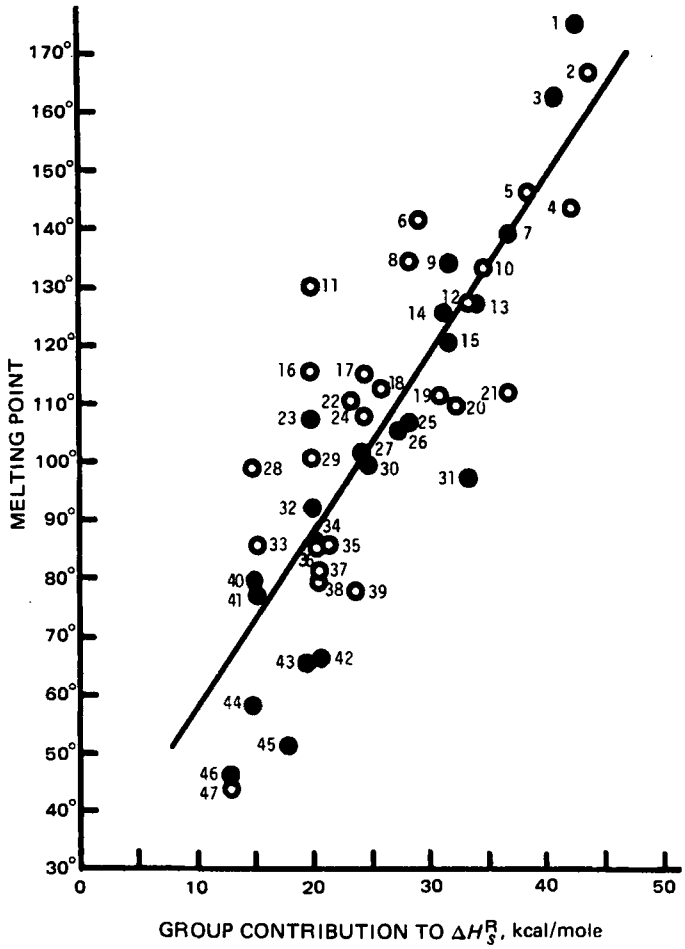


Figure 1—*Plot of melting points of dinoprostone (●) and dinoprost (○) C_1-esters* versus *the group contribution of the alcoholic portion of the ester (R) to the heat of sublimation (ΔH_s^R). The following dinoprostone C_1-esters were derived from the stated parent phenols (1): 1, p,p'-benzamidophenol; 3, N-benzoyl-L-tryosine amide; 7, N-acetyl-L-tyrosine amide; 9, p-benzamidophenol; 14, p-hydroxybenzaldehyde semicarbazone; 23, p-hydroxybenzamide; 25, p-hydroxyphenylurea; 27, acetaminophen; 31, p-tritylphenol; 32, p-phenylphenol; 40, 2-naphthol; and 41, phenyl acetate. The other compounds will be identified in future articles.*

large or very small; *e.g.*, the ΔS_s values for nonadecanoic acid and acetic acid are 151.2 and 25.7 eu, respectively (3). On the other hand, following Trouton's rule, we approximate $\Delta S_v \sim 21$ eu for pure liquids. Thus:

$$\Delta S_f^{R} = \text{constant} \qquad \text{(Eq. 5a)}$$

or:

$$\Delta S_f^{PG} + \Delta S_f^{R} = \text{constant} \qquad \text{(Eq. 5b)}$$

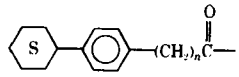
In reality, the combination of these two independent considerations supports the assumption that ΔS_f in Eq. 1 is constant for these esters. Now Eq. 2 becomes:

$$T_m = \alpha + \beta \sum_{i=1}^{n} \Delta H_i \qquad \text{(Eq. 6)}$$

where the summation operates over each functional group present in the R group.

Since no extensive group contribution data on ΔH_f are available in the literature and since ΔH_f is approximately proportional to the heat of sublimation (ΔH_s) in a series of compounds (2), we explored a relationship between the melting points of prostaglandin C_1-esters consisting of

Table II—Prednisolone C_{21}-Esters of



n	Melting Point
0	242°
1	202–203°
2	190–191°
3	160–162°

para-substituted phenyl and substituted alkyl moieties and the sum of ΔH_s contributions of each functional group present in the R moiety in the ester. Some important ΔH_s values used in our study are shown in Table I (2). A straightforward additivity rule was applied in calculating ΔH_s contributions from the R group. For instance, for the *p*-benzamidophenyl ester of dinoprostone, the ΔH_s contribution of the phenolic moiety is the sum of 2 × 10.0 for phenyl, 6.5 for >C=O, and 5.6 for —NH—, giving 32.1 kcal/mole.

The relationship between the melting points of 22 dinoprostone C_1-esters and 25 dinoprost C_1-esters and the ΔH_s contribution of the R groups is shown in Fig. 1. A least-squares analysis resulted in a slope of 3.04°/kcal/mole of ΔH_s and an intercept, the physically meaningless melting point of the prostaglandins without a proton at C_1, of 26.7°. Although the melting points of dinoprostone (63.4°) and dinoprost (~35°) are rather removed, visual inspection of the plot gives no indication of two separate relationships. The correlation coefficient was 0.851, which is surprisingly good considering all of the assumptions and approximations involved.

The reasonably good correlation observed appears to reflect the validity of our basic assumption that the prostaglandin group contribution to the melting point is constant. Both the E and F series of prostaglandins have substantial intramolecular interactions between two alkyl chains in the solid state (4) and the C_1-substituents probably do not disturb this basic molecular conformation, resulting in a rather constant crystal packing arrangement of the esters.

Of the C_1-esters prepared, about 20% of the liquid esters are predicted to be solids. Since it was difficult to crystallize many of the esters (up to 2 weeks of manipulation was sometimes required), many of these liquid esters possibly could be crystallized under proper conditions. Although we attribute the deviations observed largely to assumptions in the analysis, they could originate from polymorph formation. All of the esters were carefully purified by silica gel column chromatography, and it is unlikely that the deviations were due to impurities.

The present analysis applies mainly to terminally substituted prodrugs such as the prostaglandin C_1-esters. Application of the additivity principle may not hold for other prodrugs where the modification is at an internal position. Under these conditions, the assumption that ΔS_f is constant is not warranted due to a significantly higher entropy contribution (mainly rotational) brought about by modification at an internal position. This situation is illustrated by the *decrease* in melting points observed in some prodrug series using internal homologation (Table II). This decrease probably is due to an additional increase in entropy, which would lower T_m (Eq. 1). Therefore, our group contribution approach is not applicable in this case.

Cautious application of the treatment to terminally substituted prodrugs of relatively constant size should be of great use in analyzing the influence of structure on melting points. In these special prodrug series, the melting points may now allow *a priori* estimates of the influence of structure on other related physical properties.

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Noncompartmental Determination of the Steady-State Volume of Distribution

Keyphrases □ Volume of distribution—steady state, noncompartmental determination, calculations □ Pharmacokinetics—steady-state volume of distribution, noncompartmental determination, calculations

To the Editor:

Up to the present time, the use in pharmacokinetics of the steady-state volume of distribution (Vd_{ss}) has been limited to specific compartmental mammillary models. However, mathematical methods usually associated in medicine with the use of indicator dilution curves to determine cardiac output and with the determination of mean residence time of endogenous substances following radiolabeled tracer injection permit Vd_{ss} determination without the assumption of a specific compartment model (or its analog, the assumption of a specific number of exponential functions).

Riggs (1) introduced the use of an overall volume of distribution term, Vd_{ss}, defined specifically with respect to the two-compartment open model, with elimination taking place from the central compartment:

$$Vd_{ss} = \left(1 + \frac{k_{12}}{k_{21}}\right) V_1 \qquad \text{(Eq. 1)}$$

The steady-state volume of distribution, as defined by Riggs (1), equals the total quantity of drug in the body divided by the concentration in the reference region of the central compartment when these measurements are taken when the tissue compartment contains the maximum amount of drug. Riegelman *et al.* (2) presented an exten-

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