Relative Aqueous Stabilities of Dinoprostone Free Acid (Prostaglandin E_2) and Its Carbamoylmethyl Ester

Keyphrases □ Dinoprostone—free acid and carbamoylmethyl ester, relative aqueous stabilities, effect of pH □ Stability, aqueous—dinoprostone free acid and carbamoylmethyl ester, effect of pH □ Prostaglandins—dinoprostone free acid and carbamoylmethyl ester, relative aqueous stabilities, effect of pH □ Oxytocic agents—dinoprostone free acid and carbamoylmethyl ester, relative aqueous stabilities, effect of pH

To the Editor:

We wish to report that C_1-esters of dinoprostone (prostaglandin E_2) do not provide an aqueous solution stability advantage over dinoprostone at mildly acidic pH but do provide a measurable improvement at pH > ~5.0. These findings lead to interpretations of the mechanism of dehydration of the E family of prostaglandins.

Recent publications (1, 2) treated the dehydration reaction of such prostaglandins, a degradation that occurs readily because of the labile β-hydroxy keto system in the C-8–C-12 ring. The data of Monkhouse *et al.* (1) revealed that the dehydration rate constant of dinoprostone was greater than that for prostaglandin E_1 in the pH 3–10 region, whereas the two prostaglandins showed equal stability at pH < 3. This difference was considered to be connected with the presence or absence of the C-5–C-6 double bond, which controlled the availability of some component of that side chain to the reaction site. Furthermore, these investigators ruled out the possibility of intramolecular general acid catalysis by the carboxyl group. The rate equation of Thompson *et al.* (2) included terms for specific acid and base catalyses, water catalysis, and general base catalysis.

We performed some kinetic studies comparing the stability of 0.00142 *M* solutions of dinoprostone and its carbamoylmethyl ester[1] (II), mp ~ 84°, under various conditions (Table I). The remaining prostaglandin was assayed in each case by quantitative extraction with ethyl acetate, followed by concentration and quantitative TLC on silica gel[2] with chloroform–methanol–acetic acid (90:5:5) as the developing solvent. Details of this assay procedure were reported previously (3).

It is apparent from Table I that removing the influence of the carboxyl group by esterification has no apparent effect on the rate constant at pH 4.0. The identical rate constants show that the ester has no advantage over the free acid in a mildly acidic medium. At pH 6, where dinoprostone exists mainly as the carboxylate anion, the ester shows a significant increase in stability. This increase is, however, not practical in terms of improving long-term prostaglandin stability in aqueous solution.

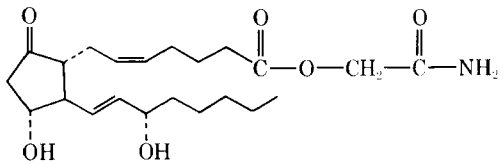
The following conclusions can be made from these findings. The pH 4.0 data show that general acid catalysis does not contribute measurably to the dinoprostone dehydration reaction. Because the pH–rate constant profile for dinoprostone "bottoms out" at pH 3–4 (2), water catalysis probably is occurring in the pH 4.0 region. The degradation rate, otherwise dependent only on specific acid catalysis at pH 3–4, would be much lower. The difference between dinoprostone and its carbamoylmethyl ester at pH 6.0 demonstrates intramolecular general base catalysis by the carboxylate anion.

From the comparative data generated by adding acetate anion (Table I) as a similar, but intermolecular, general base catalyst, it may be seen that the intramo-

Table I—Rate Constants for Dinoprostone (I) and Its Carbamoylmethyl Ester (II) in pH 4.0 (0.1 *M* Citrate) and 6.0 (0.1 *M* Phosphate) Buffers under Various Conditions ($C_0 = 1.42 \times 10^{-3}$ *M*)

Compound	pH	Temperature	Rate Constant, hr^{-1}	Comment
I	4.0	70°	0.125 ± 0.0019	—
II	4.0	70°	0.123 ± 0.013	—
I	6.0	70°	0.228 ± 0.0072	$\frac{k_I}{k_{II}} = 1.49$
II	6.0	70°	0.153 ± 0.0031	
I	6.0	60°	0.0817 ± 0.0028[a]	$\frac{k_I}{k_{II}} = 1.49$
II	6.0	60°	0.0547 ± 0.0024	
II	6.0	70°	0.317 ± 0.0045	1.0 *M* acetate anion included in 0.1 *M* phosphate medium
II	6.0	70°	0.213 ± 0.0069	0.4 *M* acetate anion included in 0.1 *M* phosphate medium
I	6.0	60°	0.0829 ± 0.0132[b]	1.0 *M* NaCl included in 0.1 *M* phosphate medium

[a] Two runs. [b] Four runs.



II

[1] Supplied by W. Morozowich, The Upjohn Co.
[2] UNIPLATES, 250-μm Silica Gel GF, Analtech Corp., Newark, DE 19711

lecular carboxylate effect (bulk concentration = 1.4×10^{-3} M) is probably a couple of orders of magnitude more efficient (4) than intermolecular carboxylate (concentration = 0.4–1.0 M). This finding is also consistent with the relative nondependence of the overall degradation rate constant of dinoprostone on concentration.

No attempt was made to equalize the ionic strengths of the media in these experiments, particularly those determining the effect of added acetate. As Table I shows, addition of 1.0 M NaCl makes no significant difference in the observed rate constant at pH 6.0. More detailed findings will be related in a subsequent report.

(1) D. C. Monkhouse, L. VanCampen, and A. J. Aguiar, *J. Pharm. Sci.*, **62**, 576(1973).

(2) G. F. Thompson, J. M. Collins, and L. M. Schmalzried, *ibid.*, **62**, 1738(1973).

(3) T. J. Roseman, B. E. Sims, and R. G. Stehle, *Am. J. Hosp. Pharm.*, **30**, 236(1973).

(4) M. L. Bender and L. J. Brubacher, "Catalysis and Enzyme Action," McGraw-Hill, New York, N.Y., 1973, p. 63ff.

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BOOKS

REVIEWS

Pharmacy and the Law. By CARL T. DeMARCO. Aspen Systems Corp., 20010 Century Blvd., Germantown, MD 20767, 1975. 381 pp. 16 × 24 cm. Price $19.50.

Carl DeMarco has filled a void in pharmacy literature with the publication of this book on pharmacy law. It is a descriptive and interpretive text on the many legal considerations involved with pharmacy practice. An analysis of pharmacy laws and legal issues of current interest is skillfully presented.

The book is divided into four parts. Part I is concerned with the professional practice of pharmacy. Topics of interest to practicing pharmacists as well as students include standards of practice, drug product selection, quality assurance, and the legal aspects of clinical pharmacy. The chapter on standards of practice and a subsequent chapter on negligence contain relevant information on standards with which today's pharmacist is expected to comply. A section on licensure requirements and operating a pharmacy highlights the North Dakota case on pharmacy ownership. Supportive personnel are discussed along with the licensure requirements of a pharmacist.

Drug laws are discussed in Part II. Of interest is a section on the dispensing of a drug for an "unofficial" or "nonapproved" use or dose. Pharmacy applications of the Federal Food, Drug and Cosmetic Act are mentioned. In addition, sections of this act are included in the appendix for those who wish to further examine it.

Part III deals solely with controlled substances. Since failure to comply with the many specific rules of the Controlled Substances Act can result in violation of the law, the author presents an interpretation of the requirements in addition to a copy of a selected section of this act.

Part IV covers professional liability. Various types of liabilities, including malpractice, are presented in a most understandable format. References to specific court cases and to regulations clarify the legal terms and the laws of interest to pharmacists.

A combination of background material, court cases, laws, regulations, and the author's interpretations make this an interesting and informative text. Drug laws and the regulation of drug use control inevitably undergo change. Hence the book will be outdated without periodic supplements or frequent revisions. The author has made a contribution in this well-written text. It should be of interest to practicing pharmacists and students of pharmacy law because it is completely understandable to the nonattorney. It should serve as an excellent reference source book and as a textbook.

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Pharmacokinetics. Pharmacy and Related Subjects Series. Vol. 1. By MILO GIBALDI and DONALD PERRIER. Dekker, 270 Madison Ave., New York, NY 10016, 1975. 329 pp. 16 × 24 cm. $19.50.

As a textbook, the choice of topics is excellent and the order of presentation is logical. As a reference source, the reader may find it selectively parsimonious.

There are nine chapters and appendixes in this volume. The subject is introduced through modeling of linear systems of increasing complexity (Chapters 1 and 2). The techniques developed are then applied to study kinetic behavior on multiple dosing and to estimate drug bioavailability (Chapters 3 and 4). The concept of volumes of distribution is discussed in Chapter 5. The remaining chapters may be considered special topics, which include the kinetics of pharmacologic response, nonlinear systems, and the effect of route of administration and of renal impairment on drug disposition. The fact that step-by-step derivations of mathematical expressions are given throughout may be helpful to some but distracting to others.

Even though a glossary of terms is included, duplications remain. For example, the variable t is used to represent real time, time from the last dose, and time after an infusion. The definition of β as the "apparent first-order elimination rate constant for a drug that confers upon the body the characteristics of a multi-compartment model, obtained from the terminal slope . . . " may be less than universally acceptable. While β may be shown to be a constant of proportionality between the disappearance rate and the amount of drug in the body during the log-linear phase, this particular usage is valid only some of the time. For all times, β is a function of drug distribution as well as elimination.

By their recurrence, perhaps greater importance has been ascribed to the assumption concerning the completeness of absorption and to the idea of modeling from radioactivity data of unknown chemical composition than they deserve. In both cases, the practical limitations are formidable in actual usage. On the other hand, the material in Chapter 8 on the route of administration and drug disposition may be difficult for the uninitiated without a fuller discourse of alternative views, at least in reference.

When read in perspective, particularly in the prescribed sequence, this volume is a valuable teaching text in pharmacokinetics. It is the first of its kind in English and fulfills a critical need at an intermediate level between elementary and encyclopedic.

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