pH Partition Behavior of Ampicillin

Keyphrases □ Partition coefficients—ampicillin in aqueous buffer–octanol systems, effect of pH □ Ampicillin—partition coefficients in aqueous buffer–octanol systems, effect of pH □ pH—effect on partition coefficients of ampicillin in aqueous buffer–octanol systems □ Antibacterials—ampicillin, partition coefficients in aqueous buffer–octanol systems, effect of pH

To the Editor:

The pH partition behavior of the ampholytic β-lactam antibiotics ampicillin, cephalexin, and cephaloglycin was previously studied in aqueous buffer–1-octanol and aqueous buffer–1-butanol systems (1). The results obtained for ampicillin in both systems appeared to indicate that the anion was the partitioning species. Over the pH 4.9–7.9 range, apparent partition coefficients increased with pH. Apparent partition coefficient values for ampicillin in aqueous octanol were calculated after spectrophotometric analysis of only the aqueous phase and ranged from 0.18 to 0.31. These values were nearly an order of magnitude greater than the apparent partition coefficient values reported for ampicillin in water–ethyl acetate (2). In contrast, the partition coefficient values for penicillin G in water–octanol or water–ethyl acetate only differed by a factor of about 1.5 (3). The purpose of this study was to obtain reproducible partition coefficient values for ampicillin based on analyses of both the aqueous and organic phases.

Buffered solutions of ampicillin were prepared at 2 mg/ml. Twenty milliliters of both the buffer and octanol were pipetted into a container suitable for shaking. In some cases, each phase was presaturated with the other. The samples were shaken[1] mechanically for 20 min at 200–300 cpm and then centrifuged.

The octanol phase was withdrawn and transferred to a separator, where any carried-over aqueous phase was separated and discarded. Then the octanol was extracted with one 20-ml and two 10-ml portions of pH 5.2 buffer containing copper sulfate (4). These buffer portions were combined and diluted to volume in a 50-ml volumetric flask using the prepared pH 5.2 buffer. This solution was analyzed to determine the organic phase concentrations.

The aqueous phase was analyzed after dilution of a 0.3-ml aliquot with pH 5.2 buffer containing copper sulfate to 25 ml in a volumetric flask.

Analysis was by a copper catalyst procedure (4) in which the absorbance difference between the maximum near 320 nm and the baseline at 390 nm was determined from a spectrophotometric[2] recording. The concentration of each solution was calculated using a calibration curve obtained with standard solutions. Total recovered ampicillin was calculated by summing the amounts found in each solvent phase. Recovery was 100 ± 5% for the samples handled by one chemist. A slightly broader variation was noted for samples handled by another chemist.

Table I—Aqueous Buffer–Octanol Apparent Partition Coefficient Values for Ampicillin at 25°

pH	Apparent Partition Coefficient × 10^3	n
3.0	8.3	2
5.0	7.4	2
	6.2[a]	2
7.0	7.4[a]	2
	8.2	10
7.2	8.0	3
7.9	8.2	2
	6.4	2

[a] Determinations made by a second chemist.

The apparent partition coefficient was calculated by dividing the organic phase concentration by the aqueous phase concentration:

$$\text{partition coefficient} = \frac{[\text{ampicillin}]_{\text{octanol}}}{[\text{ampicillin}]_{\text{water}}} \qquad \text{(Eq. 1)}$$

The results obtained in the pH 3.0–7.9 range at 25° are shown in Table I. Contrary to previous reports, no change in the apparent partition coefficient with pH was observed.

Temperature may affect the observed partition coefficient values. However, for ampicillin in aqueous buffer–octanol systems at 25 and 37°, differences were insignificant. At pH 5.1 and 7.0 at 37°, the apparent partition coefficients were 8.3×10^{-3} and 7.3×10^{-3}, respectively, based on two determinations at each pH.

The precision and accuracy of the analytical procedure for each phase were determined, and the apparent partition coefficients were calculated. First, a spiked octanol solution, extracted with buffer as previously described, gave a mean total recovery (n = 6) of 95.5% with a range of 92.8–97.6% and a coefficient of variation of 2.0%. After partitioning, the coefficient of variation values of 0.97 and 21% were obtained for aqueous phase and organic phase concentrations, respectively. Thus, determination of the apparent partition coefficient values gave a coefficient of variation of 21% too. These values were calculated for duplicate determinations on 5 consecutive days. The poor precision probably resulted from poor phase separation, which has the greatest effect on the determination of the organic phase concentration. Therefore, a significant variation in the apparent partition coefficient value resulted.

Other factors evaluated included the time of mixing and presaturation of each phase with the other. Neither mixing time in the 10–160-min range nor presaturation of phases appeared to affect the results.

The results indicate that the extent of ampicillin partitioning in aqueous buffer–octanol systems is significantly less than had been reported earlier and is apparently unaffected by pH in the 3.0–7.9 range.

[1] Eberback Co., Ann Arbor, Mich.
[2] Cary model 14 or Perkin-Elmer model 402.

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(2) J. P. Hou and J. W. Poole, *ibid.*, **58**, 1510 (1969).
(3) A. Leo, C. Hansch, and D. Elkins, *Chem. Rev.*, **71**, 604 (1971).
(4) J. Smith, G. Degrey, and V. Patel, *Analyst*, **92**, 247 (1967).

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BOOKS

REVIEWS

The *Catharanthus* Alkaloids. Edited by W. I. TAYLOR and N. R. FARNSWORTH. Dekker, 270 Madison Ave., New York, NY 10016, 1975. 323 pp. 16 × 32.5 cm. Price $29.50.

This valuable book for students, teachers, researchers, and clinicians interested in the pharmacognosy of the *Catharanthus* alkaloids opens with a concise and significant introduction by Gordon H. Svoboda, in which he outlines the history and discovery of the outstanding alkaloid pair, vinblastine and vincristine. Dr. Svoboda, responsible for much of this research, reviews the scientific and medical aspects of these and other *Catharanthus* alkaloids in terms of their biological specificity and their relative clinical merit.

The book includes chapters dealing with the following topics: a Synopsis of the Genus *Catharanthus* (William T. Stearn, British Museum), the Photochemistry and Pharmacology of *Catharanthus roseus* (G. H. Svoboda and D. A. Blake), the Phytochemistry of the Minor *Catharanthus* Species (M. Tin-Wa and N. R. Farnsworth), Structure Elucidation and Chemistry of the Bis *Catharanthus* Alkaloids (D. J. Abrahams), the Biosynthesis of *Catharanthus* Alkaloids (R. J. Parry), and Tissue Culture Studies of *Catharanthus roseus* (David P. Carew). The final chapters, dealing with Biochemistry (William A. Creasey) and the Clinical Aspects of the Dimeric *Catharanthus* Alkaloids (R. C. DeConti and W. A. Creasey), comprehensively and thoroughly review these important topics.

The book is well organized; tables, figures, and text are of professional quality; and, in spite of the many botanical terms used, the number of misprints is remarkably small, a rare exception being a twice misspelled catharanthine (I) (p. 128).

The total amount of multidisciplinary information contained in this monograph is considerable. The book, therefore, constitutes a valuable reference work for diverse professionals needing reliable information. The authors all have worked extensively in their various specialties, thus endowing the book with an authoritative quality. In particular, the chapter on clinical effects of vinblastine and vincristine as well as other alkaloids of lesser efficacy summarizes the relative and specific clinical activity in a clear and comprehensive manner. For researchers not having easy access to detailed medical literature in this area, this chapter by DeConti and Creasey constitutes a good source for reliable information on clinical usages of currently available oncolytic *Catharanthus* alkaloids.

The only regret felt during the reading of various chapters, especially those dealing with topics presently in an active state of investigation, is in the time lag during writing and publication. Few references beyond 1972 are included in most chapters. Much excellent work during the following years thus remains unmentioned through no fault of authors or publishers.

In summary, the editors have made an excellent selection of topics and authors. The resulting book summarizes available information on this important class of alkaloids in a most readable and reliable manner. The book is heartily recommended for readers wanting to become acquainted or reacquainted with the chemistry or biology of these complex herbal products of outstanding medicinal value.

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Pro-drugs as Novel Drug Delivery Systems. Edited by T. HIGUCHI and V. STELLA. American Chemical Society, 1155 16th Street, N.W., Washington, DC 20036, 1975. 245 pp. 16 × 24 cm. Price $13.50.

This volume is a collection of papers presented during a symposium on prodrugs held in Atlantic City, September 10, 1974, under the sponsorship of the ACS Division of Medicinal Chemistry. The book consists of six sections. The first section, which constitutes approximately half of the volume, is a review of the basic concepts and approaches to the design of prodrugs. The second section covers applications of the prodrug approach to antibiotics. The remainder of the volume describes, in the form of research papers, chemical and biological studies on prodrug candidates performed in the laboratories of the authors. These chapters deal with prodrugs of phenytoin (diphenylhydantoin) and epinephrine and with the use of prodrugs in the formulation of cytotoxic agents for parenteral administration.

Although the enzymatic and some biological aspects, which are important in the design of new prodrugs, are not discussed, this book represents an excellent compilation of data on the subject. The extensive bibliography, particularly of the first two sections, and the excellent examples selected to illustrate the chemical approaches to the problem of drug delivery should make this volume a valuable addition to the library of every researcher in this field.

The book is easily readable and is recommended to graduate students and faculty of both chemistry and pharmacy. The material described in this book by the authors, who are experts in this field, ought to stimulate greatly the thinking of those who are seeking new ideas in the application of chemistry to biology and pharmacy.

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The Effect of Disease States on Drug Pharmacokinetics. Edited by LESLIE Z. BENET. American Pharmaceutical Association, 2215 Constitution Ave. N.W., Washington, DC 20037, 1976. 252 pp. 15.5 × 23 cm. Price $9.25 (APhA Member Rate, $6.50).

"The Effect of Disease States on Drug Pharmacokinetics" is a collection of the papers presented at the April 1976 symposium sponsored by the Academy of Pharmaceutical Sciences of the American Pharmaceutical Association. The 29 contributors to this symposium are among the most prominent researchers in the field of clinical pharmacokinetics.

The introduction is a general orientation to the subject and a brief discussion of various possible approaches to the investigation of potential pharmacokinetic changes. The book is divided into four parts, each of which contains one chapter that discusses the subtopic in general and one or more chapters that deal with specific examples.

In the first section, Body Perfusion, Chapter 2 presents an overview of pharmacokinetics in disease states that modify blood flow and organ perfusion. Chapter 3 deals specifically with the effects of cardiac failure on GI absorption.