product was isolated as the trihydrochloride according to the procedure for III. It was then carboxymethylated according to the procedure for V.

(Carboxymethyl)iminobis(ethylenenitrilo)tetraacetic Acid Dianhydride[6] (XV)—Compound I (39.3 g, 0.10 mole) was suspended in pyridine (50 g), and acetic anhydride (40.8 g, 0.40 mole) was added. The mixture was heated at 65° for 24 hr. The product was filtered, washed with acetic anhydride and ether, and dried.

REFERENCES

(1) J. R. Evans, R. W. Gunton, and R. G. Baker, *Circ. Res.*, **16**, 1(1965).

(2) R. W. Gunton, J. R. Evans, and R. G. Baker, *Amer. J. Cardiol.*, **16**, 482(1965).

(3) F. J. Bonte, K. D. Graham, and J. G. Moore, *Radiology*, **108**, 195(1973).

(4) R. Richards, "Radioactive Pharmaceuticals," CONF-651111, Atomic Energy Commission, 1966, pp. 323–334.

(5) W. C. Eckelman and P. Richards, *J. Nucl. Med.*, **13**, 202(1972).

(6) P. E. Valk, C. A. Dilts, and J. McRae, *ibid.*, **14**, 235(1973).

(7) W. C. Eckelman and P. Richards, *ibid.*, **11**, 761(1970).

(8) J. F. Klopper, W. Hauser, and H. L. Atkins, *ibid.*, **13**, 107(1972).

(9) J. H. Bragdon and R. Gordon, Jr., *J. Clin. Invest.*, **37**, 574(1958).

(10) C. L. Malmendier, *ibid.*, **41**, 185(1962).

(11) R. J. Blair, W. H. Beierwaltes, and L. M. Lieberman, *J. Nucl. Med.*, **12**, 176(1971).

(12) L. F. Larinov, S. A. Degteva, and N. A. Lesnaia, *Vop. Onkol.*, **8**, 12(1962).

(13) S. A. Degteva, *ibid.*, **10**, 52(1964).

(14) M. E. Wall, G. S. Abernethy, and F. I. Carroll, *J. Med. Chem.*, **12**, 180(1969).

(15) A. Badinand, A. Boucheule, and C. Charbonnier, *Soc. Chim. Fr., Bull., 5 Ser.*, **1960**, 382.

(16) W. S. Lennon, U.S. pat. 3,497,535 (1970); through *Chem. Abstr.*, **72**, P120264X(1970).

(17) V. F. Vasil'eva, O. Y. Lavrova, and N. M. Dyatlova, *Zh. Obshch. Khim.*, **36**, 724(1966).

(18) A. Vanyolos, *Rev. Chim. (Bucharest)*, **6**, 378(1955); through *Chem. Abstr.*, **50**, 16671f(1956).

(19) F. Münz, U.S. pat. 2,130,505 (1938).

[6] DTPA dianhydride.

ACKNOWLEDGMENTS AND ADDRESSES

Received July 18, 1974, from the *Department of Nuclear Medicine, Washington Hospital Center, Washington, DC 20010, and the ‡Department of Radiology, George Washington University, Washington, D.C.

Accepted for publication October 8, 1974.

Adapted from a dissertation to be submitted by S. M. Karesh to the Graduate School, University of Maryland, in partial fulfillment of the Doctor of Philosophy degree requirements.

Supported in part by the Research Foundation of the Washington Hospital Center, the Women's Auxillary of the Washington Hospital Center, and National Institutes of Health Grant GM 16262.

The authors thank Dr. W. J. Rzeszotarski and Dr. A. Mauger for many helpful discussions. This work was performed at the George Hyman Memorial Research Building.

[x] To whom inquiries should be directed (at the Washington Hospital Center).

COMMUNICATIONS

Nonclassical Phase Transfer Behavior of Phenylbutazone

Keyphrases □ Phenylbutazone—nonclassical phase transfer behavior, pH and buffer effects, dissolution and ionization rates □ Dissolution—phenylbutazone, nonclassical phase transfer behavior □ Ionization—phenylbutazone, nonclassical phase transfer behavior

To the Editor:

Lovering and Black (1, 2) recently alluded to the nonclassical behavior of phenylbutazone in its transfer through a dimethylsiloxane membrane and through an everted rat intestine as a function of pH.

I measured the ionization rates of phenylbutazone in aqueous buffered solution (μ = 0.1) at 25 ± 0.2° using a stopped-flow spectrophotometer[1] and found the protonation of the phenylbutazone anion and the deprotonation of phenylbutazone to be *noninstantaneous*[2]. As expected, both protonation and deprotonation were highly dependent on the pH of the solution as well as buffer concentration.

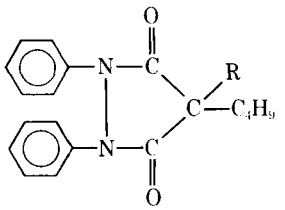
As an example, the half-life for the deprotonation of phenylbutazone (taken to zero buffer concentration) at pH 5.5 was 55 msec and it was 67 msec at pH 7.0. The half-life for protonation at pH 3.5 was 10.3 msec, while at pH 4.0 it was 22.6 msec. Phenylbutazone is a carbon acid[3] of pKa 4.50–4.70 (3–5), and the ionization rates of carbon acids are slow relative to the approximately diffusion-controlled ionization rates of other acids (6–10).

Apart from the phase transfer anomalies noted here, the chemical properties of carbon acids often show anomalies when compared to other acids. For example, carbon acids show large negative deviations

[1] Durrum stopped-flow spectrophotometer with a thermostated cell and syringes maintained at 25 ± 0.2°.

[2] The word noninstantaneous is used to describe phenomena taking place at rates considerably slower than the diffusion-controlled limit of $\sim 2 \times 10^{10}$ M^{-1} sec^{-1}.

[3] Carbon acids are acids in which the dissociating proton is bound to a carbon atom instead of a heteroatom such as oxygen or nitrogen.



I: R = H
II: R = D

in Brønsted acid–base catalysis plots when compared to carboxylic acids, phenols, and other acids (13). These negative deviations also have been directly attributed to the fact that the protonation and deprotonation rates of carbon acids are slow relative to the approximately diffusion-controlled ionization of other acids (13). The reasons for these slow ionization rates are adequately discussed elsewhere (7).

Based on this realization of noninstantaneous ionization rates, I postulated that the carbon acid, phenylbutazone, may have a hindered dissolution due to simultaneous reversible noninstantaneous chemical reaction which must take place in the aqueous diffusion layer if the dissolution involves rate-determining diffusion through the aqueous diffusion layer. By hindered, I mean that the dissolution rate at pH's greater than the pKa of the compound could not be accounted for on the basis of the Noyes–Whitney equation when applying the appropriate correction for the ionization constant (11):

$$\left(\frac{dC}{dt}\right)_0 = K'C_0\left(1 + \frac{[H^+]}{K_a}\right) \qquad \text{(Eq. 1)}$$

where $(dC/dt)_0$ is the initial rate of dissolution; K' is a constant encompassing diffusivity, surface area, and diffusion layer thickness along with any corrections for the hydrodynamics of the system under study; C_0 is the saturation solubility of the free acid form of the solid; K_a is the dissociation constant of the acid; and $[H^+]$ is the hydrogen-ion concentration. The obvious limitations of this equation have been adequately discussed (11, 16). Ideally, the comparison here should be made to a model of an acidic drug undergoing dissolution with simultaneous instantaneous chemical reaction.

Other phase transfer phenomena that involve rate-determining diffusion through an aqueous diffusion layer and a simultaneous noninstantaneous reaction (reversible in the present case) are affected by the speed of such a reaction. In Lovering and Black's study (1, 2), the time-dependent interconversion of phenylbutazone to phenylbutazone anion and vice versa necessary for the phenylbutazone to pass into and out of the dimethylsiloxane membrane, as well as transfer through the aqueous diffusion layers, is a function of the pH and concentration of buffer components in the two respective compartments. At pH >4.5, in which Lovering and Black found the permeability coefficient to be pH dependent, the half-life for the approach to the ionization equilibrium was >30 msec; *i.e.*, the interconversions between the acid and base components took place in approximately the same time range as the residence time of the components in the diffusion layer (22). Another interesting fact was that boric acid, used as the sink buffer by Lovering and Black, also undergoes nonclassical noninstantaneous ionization behavior (12).

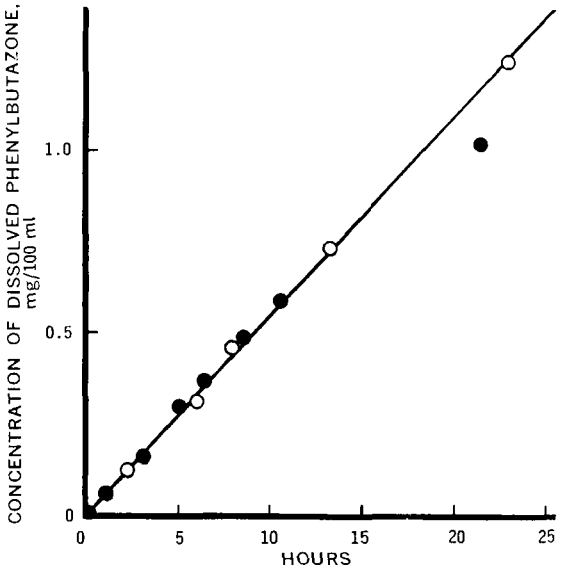


Figure 1—*Plot showing the dissolution of phenylbutazone (I, ○) and d_1-phenylbutazone (II, ●) into a 25% (v/v) ethanol–water solvent at 25°, ionic strength 0.1, pH 2.89 maintained by 0.05 M acetate buffer, from a constant-surface area pellet at a constant stirring rate of 50 rpm.*

The initial dissolution rate of phenylbutazone (I) and d_1-phenylbutazone[4] (II) into a 25% (v/v) ethanol–water solvent[5] at 25° and constant ionic strength (μ = 0.1 with sodium chloride) from a constant-surface area pellet was studied as a function of apparent pH, buffer concentration, and stirring rate. The objective of this work was to show the nonclassical behavior of phenylbutazone in the phase transport phenomenon of dissolution.

The dissolution of I and II into pH 2.89, 0.05 *M* acetate buffer and into pH 7.03, 0.05 *M* phosphate buffer is shown in Figs. 1 and 2. The identical and reproducible initial dissolution rates of I and II at pH 2.89, a pH below the pKa of phenylbutazone, represent a simple mass transfer phenomenon[6], showing that no quantitative differences in physical properties between I and II capable of affecting this simple mass transfer are present. The slower dissolution of II compared to I in the phosphate buffer (as well as the other buffers studied) can only be attributed to differences in the rate of deprotonation due to a pri-

[4] d_1-Phenylbutazone was formed by direct exchange in refluxing D_2O, mp 106°; deuteration, as determined by a Varian model T60 NMR spectrometer in $CDCl_3$, was >99% complete.

[5] Lovering and Black (1, 2) carried out all their work in purely aqueous solutions. In these ionization kinetic studies, all work again was carried out in purely aqueous media. The hydroalcoholic solvent used in the dissolution rate studies was necessary due to the poor aqueous solubility of phenylbutazone. It is recognized that a 25% (v/v) ethanol–water solvent may affect the apparent pKa of phenylbutazone (4.68 under the hydroalcoholic solutions used) and the ionization kinetics. However, it was not expected to have a major effect, especially since the dissolution rates of I and II were being compared as opposed to absolute differences. All pH values in the dissolution part of this work are apparent pH values.

[6] During this study the formation of phenylbutazone polymorphs was noted. The three polymorphs had melting points of 86, 96, and 106°, respectively. Polymorph III, mp 106°, the stable polymorph in aqueous solution, was the one studied.

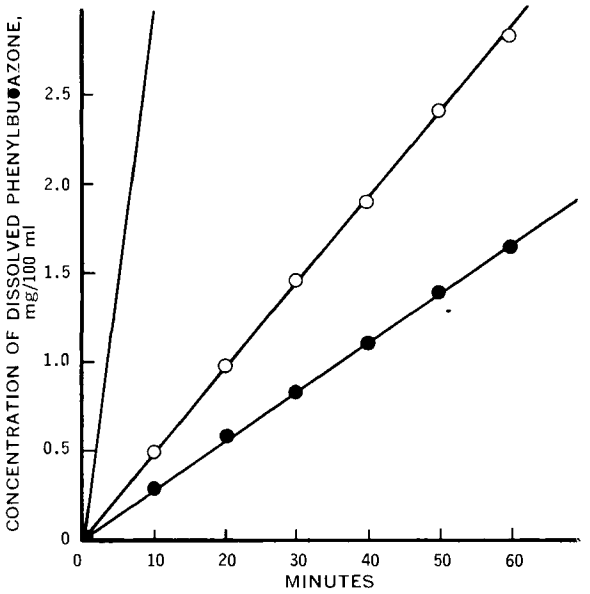


Figure 2—*Plot showing the dissolution of phenylbutazone (I, ○) and d_1-phenylbutazone (II, ●) into a 25% (v/v) ethanol–water solvent at 25°, ionic strength 0.1, pH 7.03 maintained by 0.05 M phosphate buffer, from a constant-surface area pellet at a constant stirring rate of 50 rpm. The solid line without experimental points is the line predicted by Eq. 1.*

mary isotope effect on the deprotonation rate between the two derivatives.

Also included in Fig. 2 is the theoretical line as defined by Eq. 1. It was felt that a demonstrated difference in dissolution rates between I and II at a pH greater than the pKa of phenylbutazone would be more meaningful than a comparison of the dissolution rate of I to a theoretical line, because the theoretical line itself is also model limited.

Various models have been proposed (14–18) for the dissolution of acids as a function of pH and basic components of a buffer. Similarly, theoretical models for the transport of neutral and acidic agents across theoretical membranes and the application of these models to the GI absorption of drug substances have been discussed (19–21). In all of these models, the assumption is made that all ionizations are *instantaneous, i.e.* the conversion of the acid to its basic component and vice versa take place much faster than residence times in the diffusion layer. The assumption is valid in most cases and may only be invalid in the examples noted here, namely carbon acids.

Higuchi *et al.* (22) observed the dissolution of 7-acetyltheophylline, which represents a case of dissolution with simultaneous irreversible noninstantaneous chemical reaction. They noted that increased dissolution of 7-acetyltheophylline occurred at pH's where the conversion of 7-acetyltheophylline to theophylline had a half-life of <3 sec. If the half-life was 3–30 msec or shorter, the dissolution became dependent on the diffusion of theophylline and theophyllinate from the solid–solvent interface.

The effect on dissolution behavior from solids of a reversible noninstantaneous reaction taking place within the diffusion layer film has not been formulated. Models for gas absorption accompanied by complex chemical reactions (23–28) are available, and I propose to modify these models to predict the effect of noninstantaneous reactions on the dissolution rates of solids, especially carbon acid pharmaceuticals such as oxyphenbutazone, phenindione, anisindione, diphenadione, and chlorindione.

I do not wish to imply that all anomalies in phenylbutazone behavior are directly attributed to its slow protonation and deprotonation rate. However, some of them, especially those involving phase transfer phenomena, may in part be attributed to its unusual ionization rate characteristics.

(1) E. G. Lovering and D. B. Black, *J. Pharm. Sci.*, **63,** 671(1974).

(2) *Ibid.*, **63,** 1399(1974).

(3) J. J. Burns, T. F. Yu, P. Dayton, L. Berger, A. B. Gutman, and B. B. Brodie, *Nature*, **182,** 1162(1958).

(4) R. Pulver, B. Exer, and B. Herrmann, *Schweiz. Med. Wochenschr.*, **86,** 1080(1956).

(5) H. V. Maulding and M. A. Zoglio, *J. Pharm. Sci.*, **60,** 309(1971).

(6) M. L. Bender, "Mechanisms of Homogeneous Catalysis from Protons to Proteins," Wiley–Interscience, New York, N.Y., 1971, chap. 2.

(7) M. Eigen, *Angew. Chem. Int. Ed.*, **3,** 1(1964).

(8) J. R. Jones, *Progr. Phys. Org. Chem.*, **9,** 241(1972).

(9) T. Riley and F. A. Long, *J. Amer. Chem. Soc.*, **84,** 522(1962).

(10) R. F. Pratt and T. C. Bruice, *J. Org. Chem.*, **37,** 3563(1972).

(11) L. Lachman, H. A. Lieberman, and J. L. Kanig, "The Theory and Practice of Industrial Pharmacy," Lea & Febiger, Philadelphia, Pa., 1970, pp. 246–248.

(12) N. Ingri, *Acta Chem. Scand.*, **17,** 573(1963).

(13) W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N.Y., 1969, pp. 175–178.

(14) W. Nernst, *Z. Phys. Chem.*, **47,** 52(1904).

(15) E. Brünner, *ibid.*, **47,** 56(1904).

(16) W. I. Higuchi, E. L. Parrott, D. E. Wurster, and T. Higuchi, *J. Amer. Pharm. Ass., Sci. Ed.*, **47,** 376(1958).

(17) H. Nogami, T. Nagai, and A. Suzuki, *Chem. Pharm. Bull.*, **14,** 333(1966).

(18) H. Nogami, T. Nagai, and K. Ito, *ibid.*, **14,** 351(1966).

(19) A. Suzuki, W. I. Higuchi, and N. F. H. Ho, *J. Pharm. Sci.*, **59,** 644(1970).

(20) *Ibid.*, **59,** 651(1970).

(21) N. F. H. Ho, W. I. Higuchi, and J. Turi, *J. Pharm. Sci.*, **61,** 192(1972).

(22) T. Higuchi, H. K. Lee, and I. H. Pitman, *Farm. Aikak.*, **80,** 55(1971).

(23) K. Onda, E. Sada, T. Kobayashi, and M. Fujine, *Chem. Eng. Sci.*, **25,** 753(1970).

(24) D. W. van Krevelen and P. J. Hoftizer, *Rec. Trav. Chim.*, **67,** 563(1948).

(25) P. V. Danckwerts, *Trans. Faraday Soc.*, **46,** 300(1950).

(26) G. Astarita, "Mass Transfer with Chemical Reaction," Elsevier, New York, N.Y., 1967, p. 9.

(27) D. W. van Krevelen and C. J. van Hooren, *Rec. Trav. Chim.*, **67,** 587(1948).

(28) D. W. Peaceman, Sci. D. thesis, Massachusetts Institute of Technology, Cambridge, Mass., 1951.

Valentino J. Stella

College of Pharmacy
Department of Pharmaceutical Chemistry
University of Kansas
Lawrence, KS 66044

Received August 19, 1974.

Accepted for publication December 17, 1974.

The technical assistance of S. Tamborski and J. D. Pipkin and the support for J. D. Pipkin from Interx Research Corporation are gratefully acknowledged. This work was done in part while I was on the staff of the School of Pharmacy, University of Illinois at the Medical Center, Chicago, Ill.