

variability when rates were to be compared, enough catalyst was prepared so that portions of the same catalyst could be used in each of the runs. The catalysts were dried in a vacuum desiccator over P_2O_5 for 24 hr. after which they were pulverized and mixed to insure uniformity and then stored in tightly stoppered bottles until used. The strength of the catalyst used in the various hydrogenations is indicated by, e.g., A-100, in which the A designates that the catalyst was prepared in the presence of sodium acetate, and the number indicates the milligrams of $PdCl_2$ used per gram of charcoal.

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Carbonation of Aqueous Solutions with Acid Anhydrides

Slow Acidification in Homogeneous Systems

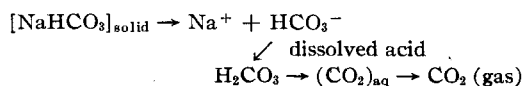
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A novel means of achieving a superior degree of carbonation by use of sodium bicarbonate and various latentiated acidifiers is presented. The physical chemical basis of the formulation depends on essentially total dissolution of the bicarbonate salt and the latentiated acidifier prior to formation of any free carbonic acid. Data are presented to show the feasibility of the use of glutaric anhydride as the acid precursor. The pH profile of hydrolysis of the anhydride and its behavior in the presence of nucleophiles such as CO_3^{2-} , HPO_4^{2-} , etc., are discussed. It is shown that a markedly greater degree of supersaturation with respect to carbon dioxide can be achieved by this route than is possible by the conventional method of dissolving sodium bicarbonate and a solid acid in water.

ALTHOUGH chemical carbonation of pharmaceutical and beverage solutions has been practiced for generations, the basic process involving acidification of bicarbonate has changed little despite the fact that present methods suffer from serious theoretical drawbacks. In practice, solid mixtures of sodium bicarbonate and organic acids such as citric and tartaric with other pharmaceutically necessary ingredients are usually added to cold water. In such systems it is practically impossible to achieve much more than an atmospheric saturation of the solution with respect to the released carbon dioxide, the excess gas normally escaping from the solution as rapidly as the ingredients dissolve. The exact geographical site where carbon dioxide is generated depends on the relative dissolution rates of

the bicarbonate and the acid particles. If the acid dissolves first, then the bulk of the reaction takes place in the saturated solution in close proximity to the undissolved bicarbonate particles. If the bicarbonate dissolves faster, the reaction takes place essentially near the surface of the undissolved acid. Such suspension systems did not favor supersaturation with respect to carbon dioxide since the particulate solids act as nuclei for bubble formation.

Thus, for the more common case in which we have the reaction



occurring largely in the vicinity of the undissolved bicarbonate particles, the rate of escape of gaseous carbon dioxide is facilitated by two factors. Since the organic acids are normally present in a substantial excess, localized areas of a high degree of supersaturation with respect to the gas form around each particle of the bi-

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carbonate. This occurs despite the fact that the average concentration may still be well below saturation. This in itself would favor the loss of the gas from the solution. The effect is further compounded by the nucleation effect of the solid particulate surface mentioned above.

It is proposed that this situation could be obviated by resorting to a system in which the acidity is generated in a uniform homogeneous manner throughout the bulk of an aqueous solution phase in which bicarbonate has already been dissolved. A high degree of supersaturation with respect to the gas would not occur at any localized point in such a system. The solution would, furthermore, be free of solid matter when the concentration of the dissolved gas rises above its solubility.

The proposed homogeneous generation of acidity can be effected in any number of ways. From the standpoint of convenience and practicality, the present study has been limited, however, to evaluation of an acid anhydride as the acid precursor. Since an anhydride is not an acid, it and sodium bicarbonate can be dissolved to form a homogeneous aqueous solution without initially reacting with each other. Only following dissolution will the anhydride hydrolyze to form acid uniformly throughout the solution with simultaneous production of carbonic acid.

For the purpose of the present study, glutaric anhydride was selected for evaluation of the concept. The compound is potentially readily available, and the acid derived from it is non-toxic and apparently suitable for food and drug purposes. Its close homologs, succinic and adipic acids, are currently employed for food purposes. The authors have discovered, moreover, that glutaric anhydride, unlike succinic anhydride, is apparently highly soluble in cold water.

As may be expected, the feasibility of this approach to carbonation from a practical point of view depends to a great extent on the rate of hydrolysis of the anhydride employed. Although the conversion should not take place instantly, it should be reasonably fast. Hydrolysis of glutaric anhydride at room temperature occurs relatively rapidly, the half-life of the reaction being of the order of a few minutes. The reaction is relatively insensitive to acids (1-5), catalytic effects becoming important only at very low pH values (about less than 1). On the other hand, the anhydride is readily attacked by nucleophiles.

In the present investigation the feasibility of the concept outlined above has been tested by determining the rate of hydrolysis of glutaric

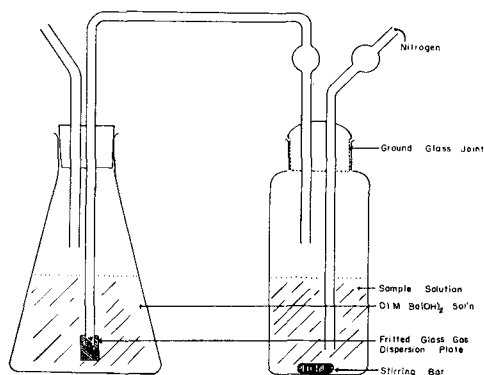


Fig. 1.—Apparatus for determining residual dissolved carbon dioxide.

anhydride in the presence of nucleophilic species which may be expected to be found in solutions formulated for this purpose. Apparent catalytic behaviors of bicarbonate, carbonate, phosphate, citrate, and acetate have been determined. In addition, the degrees of carbonation elicited by glutaric anhydride and by glutaric acid have been compared.

EXPERIMENTAL

Reagents.—Glutaric anhydride (Aldrich Chemical Co., Inc., Milwaukee, Wis.) was washed with successive portions of cold ethyl ether to remove any acid that may have been present until a melting point of $56.0 \pm 0.5^\circ$ was attained.

Dioxane was prepared after the method of Vogel (6). All remaining chemicals were of the highest grade commercially available.

Determination of Extent of Saturation Produced by Chemical Carbonation.—Equimolar amounts of glutaric acid and sodium bicarbonate were mixed as powders. A sufficient amount of the powder mixture was quickly added to 250 ml. of water at 23° in a gas washing cylinder (Fig. 1) to yield eventually 20 or 40 mmoles of carbon dioxide (corresponding to 2.23-4.45 times the solubility of CO_2 at 23°). The reaction mixture was stirred by use of a magnetic stirrer for 1 min. in the open vessel to allow for escape of carbon dioxide to the atmosphere. At the end of this time, the surface of the mixture was swept with nitrogen to remove carbon dioxide. The gas washing cylinder was then closed. By passing nitrogen through the solution for 1 hr., the carbon dioxide produced or remaining in solution was swept, along with the inert carrier gas, into 0.1 *M* barium hydroxide. The residual barium hydroxide was titrated with 0.1 *N* potassium acid phthalate, and the amount of carbon dioxide liberated was calculated.

The same procedure was repeated using glutaric anhydride instead of glutaric acid. In addition, identical conditions were maintained in experiments where the reaction time in the open vessel was allowed to get progressively longer.

Determination of Hydrolytic Rate Constants.—Buffer solutions of varying concentration were prepared. The pH was adjusted to the desired

value by addition of a saturated solution of sodium hydroxide or concentrated hydrochloric acid except for carbonate-bicarbonate which was prepared by bubbling carbon dioxide into sodium bicarbonate solution. In all cases an ionic strength of 1 was maintained with potassium chloride. A Beckman expanded scale pH meter was used for all pH measurements. The solutions were equilibrated at $27.0 \pm 0.1^\circ$. One hundred microliters of a 0.877 *M* solution of glutaric anhydride in dioxane was added directly to the spectrophotometric cells containing the buffer. The disappearance of glutaric anhydride was followed at 248 $m\mu$ on a Cary model 11 recording spectrophotometer with thermostated cell compartments. Measurements after each run indicated that the pH remained within 0.05 unit of the initial pH.

RESULTS AND DISCUSSION

Rate of Conversion of Glutaric Anhydride to Acid.—The basic principle of the proposed method depends on controlled conversion of a nonacid to an acid following dissolution. The suitability of glutaric anhydride for this purpose is evident from Table I, although from a practical standpoint a somewhat faster rate may be preferred. At room

TABLE I.—SPECIFIC RATE CONSTANTS FOR HYDROLYSIS OF GLUTARIC ANHYDRIDE^a

Temp., °C.	$k \times 10^3$ sec. ⁻¹	$t_{1/2}$ (sec.)
23.0	2.45	285
26.5	2.98	232
28.2	3.46	202
30.0	3.84	180
34.2	4.76	146
39.2	6.27	111

^a From an Arrhenius plot, the ΔH of activation was found to be 10,250 cal./mole. This value is in good agreement with that obtained from the literature (1).

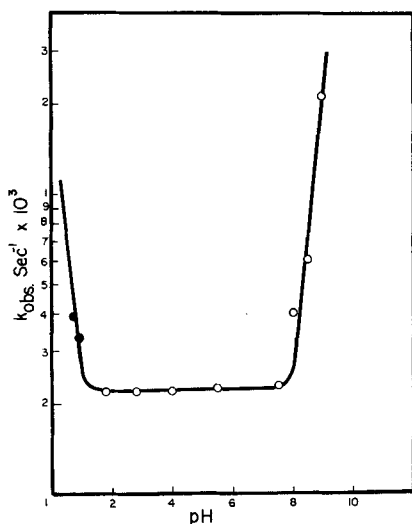


Fig. 2.—The pH profile of glutaric anhydride hydrolysis in aqueous solutions. Key: O, extrapolated limiting rate of buffer plots; ●, values obtained by direct determination.

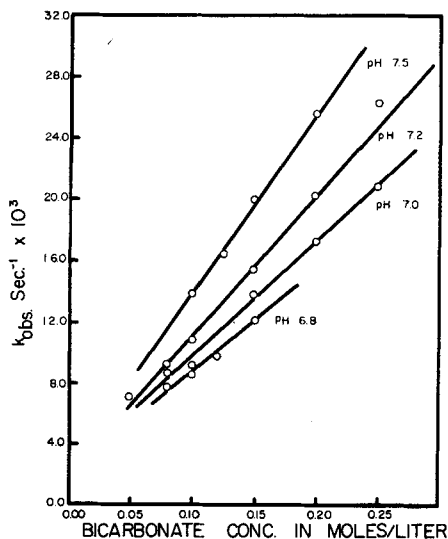


Fig. 3.—Hydrolytic rate constants as a function of molar concentration of bicarbonate buffer.

temperature the half-life of conversion is under 5 min., at 40° it is under 2 min. but is estimated to lengthen to roughly 10 min. at 10° . These results are consistent with those of earlier workers (1, 4).

It must be kept in mind that the hydrolytic reaction is largely independent of pH. The pH profile shown in Fig. 2 was obtained as a part of this study. Although there is evidence for both acid (H^+) and alkaline (OH^-) attacks on the anhydride, these occur only at pH extremities. The rate of OH^- attack measured as a part of this study is, however, substantially slower than those reported earlier (1). More complete reports on this phase will be treated in a later communication.

Nucleophilic Mediated Cleavage of Glutaric Anhydride.—Although the rate of hydrolysis of glutaric anhydride attributable to water alone is fixed at each temperature, the cleavage to acid can be accelerated by addition of nucleophilic species. The most important of these for the present purpose is that induced by the carbonate system itself.

The rate of hydrolysis of glutaric anhydride observed spectrophotometrically is shown in Fig. 3 as a function of bicarbonate concentration at several pH values. It is evident that relatively low levels of the basic species corresponding to that necessary for production of 1.5 to 4 vol. of carbon dioxide (0.05–0.15 *M*) exert profound catalytic effects. It is further evident that this phenomenon will greatly reduce the time necessary for conversion of the anhydride to the acid.

The nature of the pH dependency of the catalytic effect strongly suggests that the effective nucleophilic species is probably the doubly charged carbonate ion, not the singly charged bicarbonate. If we are to attribute the observed effect largely to the small amount of carbonate ions present, it would appear that the doubly charged nucleophile is an extremely effective catalyst for this reaction.

We have also observed that other usual nucleophiles such as acetate, phosphate (HPO_4^{2-}), citrate, etc., are effective attacking species. Details relative to these will be reported elsewhere.

TABLE II.—DEGREE OF SATURATION^a REMAINING WITH RESPECT TO CARBON DIOXIDE AS A FUNCTION OF TIME AFTER MIXING

Saturation Corresponding to Total Available CO ₂	Acidifier	Degree of Saturation			
		After 1 min.	After 2 min.	After 3 min.	After 5 min.
2.23	Glutaric acid	1.38	1.02	0.91	0.74
2.23	Glutaric anhyd.	1.94	1.78	1.65	1.26
4.45	Glutaric acid	1.39	1.11	0.97	0.83
4.45	Glutaric anhyd.	3.55	3.28	2.81	2.56

^a All measurements made at 23°. The degree of saturation was taken to be 1 when a solution yielded 0.0359 *M* of carbon dioxide. The amount of acidifier taken was equimolar in every instance.

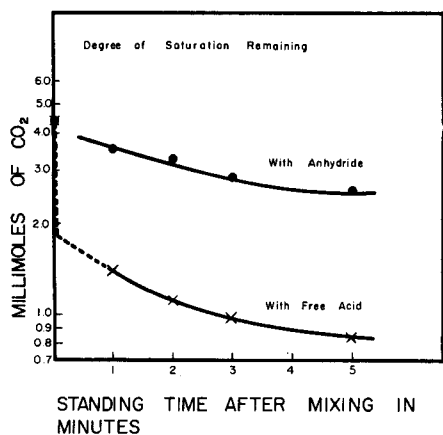


Fig. 4.—Comparison of degree of saturation of an aqueous solution using glutaric acid and glutaric anhydride.

Degree of Carbonation Produced by the System.

—The degree of saturation observed for the anhydride process is shown in Table II compared to that found when preformed acid is used. These studies were carried out by quickly adding equimolar mixture of sodium bicarbonate and acidifier powders to water and determining the amount of carbon dioxide which can be swept out of the solution after various periods of standing. For the anhydride system a completely clear solution is produced before any carbon dioxide is evolved. The data observed for the free acid are probably quite typical for what can be expected for citric or other more common acids. Although the use of quickly dissolving powder mixtures probably resulted in less of a loss of the gas than would be expected from tabulated formulation in the free acid system, copious amounts of gas were lost in these instances during the dissolution phase.

The data confirm the advantage of the anhydride formulation in eliciting high degrees of supersaturation. With free glutaric acid, the degree of satura-

tion possible is essentially the same for the two levels of the powder mixture used. With the anhydride, on the other hand, the extent of supersaturation appears to be a direct function of the total available carbon dioxide. It would appear that even greater amount of the gas can be incorporated by increasing the amount of powder used.

In Fig. 4 the residual carbon dioxide content determined after several periods of standing for both the anhydride and the acid has been plotted semilogarithmically. The loss does not occur in a first-order fashion. The exact function is probably quite complex and depends on the presence of trace particulates and impurities. It is, nevertheless, evident that the gas loss is very much less with the anhydride.

CONCLUSION

It is apparent from these studies that the approach of using nonacidic substances which rapidly convert to free acid only following dissolution of all solids affords an interesting means of achieving high degrees of chemical carbonation. The authors do not necessarily claim that the particular anhydride or even any anhydride is the optimal acid precursor for this purpose. It is possible that certain other acid producing substances such as active esters, acyl halides, etc., may prove more promising. The present contribution rests largely on the concept that the use of any such latentiated acid producer can help in formulation of self-carbonating solid pharmaceuticals.

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