

- (3) F. Bergman, "The Physical Chemistry of Enzymes," Publ. No. 20, Faraday Society, London, England, 1955, p. 126.
- (4) E. W. Gill, *Proc. R. Soc., B*, **150**, 381 (1959).
- (5) R. Wien, *Arch. Int. Pharmacodyn. Ther.*, **97**, 395 (1954).
- (6) F. G. Canepa, *Nature (London)*, **195**, 573 (1962).
- (7) H. R. Ing, P. Kordik, and D. P. H. Tudor Williams, *Br. J. Pharmacol.*, **7**, 103 (1952).
- (8) K. H. Ginzel, H. Klupp, O. Kraupp, and G. Werner, *Arch. Exp. Pathol. Pharmacol.*, **221**, 336 (1954).
- (9) G. Germain, P. Main, and M. M. Woolfson, *Acta Crystallogr.*, **A27**, 368 (1971).
- (10) P. C. Hamm and A. J. Speziale, U.S. pat. 2,864,682 (1958); through *Chem. Abstr.*, **54**, 20059h (1960).
- (11) L. Miller and M. L. Tainter, *Proc. Soc. Exp. Med.*, **57**, 262 (1944).
- (12) N. Grier and S. J. Lederer, French pat. 1,347,339 (1963); through *Chem. Abstr.*, **60**, 10693h (1964).
- (13) J. B. Hendrickson, M. L. Maddox, J. J. Sims, and H. D. Kaesz, *Tetrahedron*, **20**, 449 (1964).
- (14) D. Seyferth and G. Singh, *J. Am. Chem. Soc.*, **87**, 4156 (1965).
- (15) D. J. Martin and C. E. Griffin, *J. Org. Chem.*, **30**, 4034 (1965).
- (16) C. E. Griffin and M. Gordon, *J. Am. Chem. Soc.*, **89**, 4427 (1967).
- (17) M. J. Gallagher, *Aust. J. Chem.*, **21**, 1197 (1968).
- (18) H. J. Bestmann, H. G. Liberda, and J. P. Snyder, *J. Am. Chem. Soc.*, **90**, 2963 (1968).
- (19) F. Caesar and W. D. Balzer, *Chem. Ber.*, **102**, 1665 (1969).
- (20) H. I. Zeliger, J. P. Snyder, and H. J. Bestmann, *Tetrahedron Lett.*, **1969**, 2199.
- (21) G. P. Schiemenz and H. Rast, *ibid.*, **1969**, 2165.
- (22) G. A. Gray, *J. Am. Chem. Soc.*, **95**, 7736 (1973).
- (23) F. J. Weigert and J. D. Roberts, *Inorg. Chem.*, **12**, 313 (1973).
- (24) R. Benassi, M. L. Schenetti, F. Taddei, P. Vivarelli, and P. Dembech, *J. Chem. Soc. Perkin II*, **1974**, 1338.
- (25) M. Seno, S. Tsuchiya, H. Kise, and T. Asahara, *Bull. Chem. Soc. Jpn.*, **48**, 2001 (1975).
- (26) T. A. Albright, W. J. Freeman, and E. E. Schweizer, *J. Am. Chem. Soc.*, **97**, 940 (1975).
- (27) *Ibid.*, **97**, 2942 (1975).
- (28) A. J. Speziale and K. W. Ratts, *J. Am. Chem. Soc.*, **85**, 2790 (1963).
- (29) *Ibid.*, **87**, 5603 (1965).
- (30) F. S. Stephens, *J. Chem. Soc.*, **1965**, 5640. *Ibid.*, **1965**, 5658.
- (31) H. J. Bestmann and J. P. Snyder, *J. Am. Chem. Soc.*, **89**, 3936 (1967).
- (32) F. J. Randall and A. W. Johnson, *Tetrahedron Lett.*, **1968**, 2841.
- (33) A. J. Dale and P. Frøyen, *Acta Chem. Scand. Ser. B*, **24**, 3772 (1970).
- (34) I. F. Wilson and J. C. Tebby, *Tetrahedron Lett.*, **1970**, 3769.
- (35) H. I. Zeliger, J. P. Snyder, and H. J. Bestmann, *ibid.*, **1970**, 3313.
- (36) I. F. Wilson and J. C. Tebby, *J. Chem. Soc. Perkin I*, **1972**, 31.
- (37) M. D. Joesten and L. J. Schaad, "Hydrogen Bonding," Dekker, New York, N.Y., 1974, p. 253.
- (38) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).
- (39) M. Karplus, *J. Am. Chem. Soc.*, **85**, 2870 (1963).
- (40) R. J. Abraham and K. G. R. Pachler, *Mol. Phys.*, **7**, 165 (1964).
- (41) F. G. Canepa, *Acta Crystallogr.*, **16**, 145 (1963).
- (42) K. Lonsdale, H. J. Milledge, and L. M. Pant, *ibid.*, **19**, 827 (1965).
- (43) I. G. Marshall, J. B. Murray, G. A. Smail, and J. B. Stenlake, *J. Pharm. Pharmacol.*, **19**, 535 (1967).
- (44) H. O. J. Collier, *Br. J. Pharmacol.*, **7**, 392 (1952).
- (45) J. B. Stenlake, W. D. Williams, N. C. Dhar, and I. G. Marshall, *Eur. J. Med. Chem.*, **9**, 233 (1974).
- (46) *Ibid.*, **9**, 239 (1974).
- (47) J. B. Stenlake, W. D. Williams, N. C. Dhar, R. D. Waigh, and I. G. Marshall, *Eur. J. Med. Chem.*, **9**, 243 (1974).
- (48) P. G. Waser, *Pharmacol. Rev.*, **13**, 365 (1961).
- (49) M. Sundaralingham, *Nature (London)*, **217**, 35 (1968).
- (50) W. H. Beers and I. Reich, *ibid.*, **228**, 917 (1970).

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## General Method for Calculation of Hydrogen-Ion Concentration in Multicomponent Acid-Base Mixtures

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**Abstract** □ A generalized method for the rapid evaluation of complicated ionic equilibria in terms of the hydrogen-ion concentration was developed. The method was based on the derivation of a single general equation that could be used to evaluate any mixture. A tableau method also was developed which allowed calculation of the numerical solution to the general equation without computer analysis or graphical or intuitive approximations. Examples illustrating the utility of the method are presented. These examples include a mixture of barbital, citric acid, boric acid, monobasic sodium phosphate, and sodium hydroxide. Calculated hydrogen-ion concentrations showed good agreement with experimental values for simple and complex solutions. The major advantages of the

method are its simplicity and the obtainment of numerical solutions without initial approximations in the calculations. However, activity corrections are not included in the calculations.

**Keyphrases** □ Hydrogen-ion concentration—general calculation method for multicomponent acid-base mixtures, calculated results compared with experimental results □ Model, mathematical—calculation of hydrogen-ion concentration in multicomponent acid-base mixtures, comparison with experimental results □ Acid-base mixtures—calculation of hydrogen-ion concentration in multicomponent acid-base mixtures, comparison with experimental results

The calculation of pH values for multicomponent mixtures of weak acids and bases, strong acids and bases, and ampholytes often requires solving a formidable set of simultaneous equations. Although intuitive reasoning may lead to simplifications, it also may lead to erroneous results

(1). Although graphical procedures (2) have shown didactic and practical utility, they can become complex and the evaluation may be difficult.

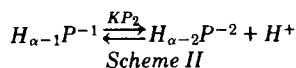
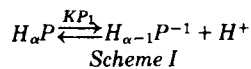
A general method for rapid evaluation of complicated equilibria in terms of the hydrogen-ion concentration is

described in this paper. A tableau method for the numerical solution also is described. This method eliminates the need for computer analysis.

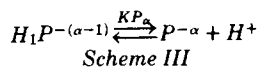
Activity coefficients were omitted in the following sections to simplify the treatment of the equilibria presented. These corrections may be needed in many pharmaceutical situations.

### THEORETICAL

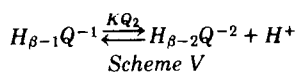
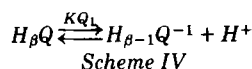
**Mixture of Weak Polybasic Acids**—Let the mixture contain a concentration  $TP$  of a weak polyprotic acid ( $H_\alpha P$ ) with  $\alpha$  dissociable hydrogen ions and a concentration  $TQ$  of a weak polyprotic acid ( $H_\beta Q$ ) with  $\beta$  dissociable hydrogen ions. The equilibrium expressions for  $H_\alpha P$  are:



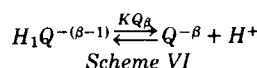
⋮



and for  $H_\beta Q$  are:



⋮



Let:

$$P_0 = H_\alpha P \quad (\text{Eq. 1})$$

$$P_1 = H_{\alpha-1} P^{-1} \quad (\text{Eq. 2})$$

⋮

$$P_\alpha = P^{-\alpha} \quad (\text{Eq. 3})$$

and:

$$Q_0 = H_\beta Q \quad (\text{Eq. 4})$$

$$Q_1 = H_{\beta-1} Q^{-1} \quad (\text{Eq. 5})$$

⋮

$$Q_\beta = Q^{-\beta} \quad (\text{Eq. 6})$$

The individual species for each acid can be expressed as functions of  $P_0$  or  $Q_0$ , the respective ionization constants, and the hydrogen-ion concentration. By using Schemes I–VI and Eqs. 1–6, the following equations can be derived:

$$P_0 = P_0 \quad (\text{Eq. 7})$$

$$P_1 = KP_1 H^{-1} P_0 \quad (\text{Eq. 8})$$

$$P_2 = KP_1 KP_2 H^{-2} P_0 \quad (\text{Eq. 9})$$

⋮

$$P_\alpha = KP_1 KP_2 \dots KP_\alpha H^{-\alpha} P_0 \quad (\text{Eq. 10})$$

and:

$$Q_0 = Q_0 \quad (\text{Eq. 11})$$

$$Q_1 = KQ_1 H^{-1} Q_0 \quad (\text{Eq. 12})$$

$$Q_2 = KQ_1 KQ_2 H^{-2} Q_0 \quad (\text{Eq. 13})$$

⋮

$$Q_\beta = KQ_1 KQ_2 \dots KQ_\beta H^{-\beta} Q_0 \quad (\text{Eq. 14})$$

Note that  $H^{-1} = 1/H$ . Let the charge balance be expressed as:

$$D = \sum_{p=0}^{\alpha} p P_p + \sum_{q=0}^{\beta} q Q_q \quad (\text{Eq. 15a})$$

where (1):

$$D = H - OH = H - \frac{K_w}{H} \quad (\text{Eq. 15b})$$

Let the mass balance for each acid be expressed as:

$$TP = \sum_{p=0}^{\alpha} P_p \quad (\text{Eq. 16})$$

and:

$$TQ = \sum_{q=0}^{\beta} Q_q \quad (\text{Eq. 17})$$

Equations 7–10 and Eqs. 11–14, respectively, can be written in general form as:

$$P_p = \prod_{\tau=0}^p KP_\tau H^{-p} P_0 \quad (\text{Eq. 18})$$

and:

$$Q_q = \prod_{\tau=0}^q KQ_\tau H^{-q} Q_0 \quad (\text{Eq. 19})$$

where  $KP_0 = KQ_0 = 1$ .

Substitution of Eq. 18 into Eq. 16 and of Eq. 19 into Eq. 17 yields, respectively:

$$TP = \sum_{p=0}^{\alpha} \prod_{\tau=0}^p KP_\tau H^{-p} P_0 \quad (\text{Eq. 20})$$

and:

$$TQ = \sum_{q=0}^{\beta} \prod_{\tau=0}^q KQ_\tau H^{-q} Q_0 \quad (\text{Eq. 21})$$

Rearrangement of Eqs. 20 and 21 yields, respectively:

$$P_0 = \frac{TP}{\sum_{p=0}^{\alpha} \prod_{\tau=0}^p KP_\tau H^{-p}} \quad (\text{Eq. 22})$$

and:

$$Q_0 = \frac{TQ}{\sum_{q=0}^{\beta} \prod_{\tau=0}^q KQ_\tau H^{-q}} \quad (\text{Eq. 23})$$

Substitution of Eq. 22 into Eq. 18 and of Eq. 23 into Eq. 19 yields, respectively:

$$P_p = \frac{\prod_{\tau=0}^p KP_\tau H^{-p} TP}{\sum_{p=0}^{\alpha} \prod_{\tau=0}^p KP_\tau H^{-p}} \quad (\text{Eq. 24})$$

and:

$$Q_q = \frac{\prod_{\tau=0}^q KQ_\tau H^{-q} TQ}{\sum_{q=0}^{\beta} \prod_{\tau=0}^q KQ_\tau H^{-q}} \quad (\text{Eq. 25})$$

Substitution of Eqs. 24 and 25 into Eq. 15a yields:

$$D = \frac{\sum_{p=0}^{\alpha} p \prod_{\tau=0}^p KP_\tau H^{-p} TP}{\sum_{p=0}^{\alpha} \prod_{\tau=0}^p KP_\tau H^{-p}} + \frac{\sum_{q=0}^{\beta} q \prod_{\tau=0}^q KQ_\tau H^{-q} TQ}{\sum_{q=0}^{\beta} \prod_{\tau=0}^q KQ_\tau H^{-q}} \quad (\text{Eq. 26})$$

Rearrangement of Eq. 26 followed by multiplication by  $H^{(\alpha+\beta)}$  yields:

$$\begin{aligned} D \sum_{p=0}^{\alpha} \sum_{q=0}^{\beta} \prod_{\tau=0}^p KP_\tau \prod_{\tau=0}^q KQ_\tau H^{(\alpha+\beta-p-q)} \\ = \sum_{p=0}^{\alpha} \sum_{q=0}^{\beta} \prod_{\tau=0}^p KP_\tau \prod_{\tau=0}^q KQ_\tau H^{(\alpha+\beta-p-q)} p TP \\ + \sum_{p=0}^{\alpha} \sum_{q=0}^{\beta} \prod_{\tau=0}^p KP_\tau \prod_{\tau=0}^q KQ_\tau H^{(\alpha+\beta-p-q)} q TQ \quad (\text{Eq. 27}) \end{aligned}$$

Define tensors:

$$H_{pq} = H^{(\alpha+\beta-p-q)} \quad (\text{Eq. 28})$$

and:

$$K_{pq} = \prod_{\pi=0}^p KP_{\pi} \prod_{\pi=0}^q KQ_{\pi} \quad (\text{Eq. 29})$$

Substitution of Eqs. 28 and 29 into Eq. 27 yields:

$$D \sum_{p=0}^{\alpha} \sum_{q=0}^{\beta} K_{pq} H_{pq} = \sum_{p=0}^{\alpha} \sum_{q=0}^{\beta} K_{pq} H_{pq} p TP + \sum_{p=0}^{\alpha} \sum_{q=0}^{\beta} K_{pq} H_{pq} q TQ \quad (\text{Eq. 30})$$

Equation 30 can be simplified by noting that the indexes  $p$  and  $q$  are repeated in the multiplication of the tensors  $K_{pq}$  and  $H_{pq}$ . Following the convention proposed by Jeffreys (3), the summation signs will be omitted and the summation will be implied (the indexes are given all possible values of  $p$  and  $q$  and the terms are added). Equation 30 can be written using this convention as:

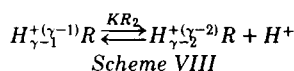
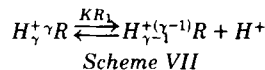
$$DK_{pq}H_{pq} = K_{p'q}H_{p'q}TP + K_{pq'}H_{pq'}TQ \quad (\text{Eq. 31})$$

where  $K_{p'q} = K_{pq}p$  and  $K_{pq'} = K_{pq}q$ .

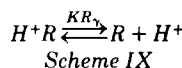
The derivation of Eq. 31 can be extended to yield an equation for any number of acids. The resulting equation is:

$$DK_{pq\dots z}H_{pq\dots z} = K_{p'q\dots z}H_{p'q\dots z}TP + K_{pq\dots z'}H_{pq\dots z'}TQ + K_{pq\dots z}H_{pq\dots z}TZ \quad (\text{Eq. 32})$$

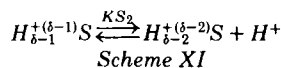
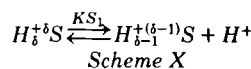
**Mixture of Weak Polyacidic Bases**—Let a mixture contain a concentration  $TR$  of a weak polyacidic base ( $H_{\gamma}^{+}R$ ) with  $\gamma$  ionizations and a concentration  $TS$  of a weak polyacidic base ( $H_{\delta}^{+}S$ ) with  $\delta$  ionizations. The equilibrium expressions for the bases are:



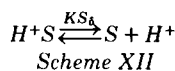
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For  $H_{\delta}^{+}S$ , they are:



⋮



Let:

$$R_0 = H_{\gamma}^{+}R \quad (\text{Eq. 33})$$

$$R_1 = H_{\gamma-1}^{+}R \quad (\text{Eq. 34})$$

⋮

$$R_{\gamma} = R \quad (\text{Eq. 35})$$

and:

$$S_0 = H_{\delta}^{+}S \quad (\text{Eq. 36})$$

$$S_1 = H_{\delta-1}^{+}S \quad (\text{Eq. 37})$$

⋮

$$S_{\delta} = S \quad (\text{Eq. 38})$$

Let the charge balance be expressed as:

$$D = \sum_{r=0}^{\gamma} (r - NR)R_r + \sum_{s=0}^{\delta} (s - NS)S_s \quad (\text{Eq. 39})$$

where  $NR$  is the number of cationic species possible from the protonation of the neutral base  $R$  and  $NS$  is the number of cationic species possible from the protonation of the neutral base  $S$ .

Let the mass balance equations be expressed as:

$$TR = \sum_{r=0}^{\gamma} R_r \quad (\text{Eq. 40})$$

and:

$$TS = \sum_{s=0}^{\delta} S_s \quad (\text{Eq. 41})$$

The individual species for each base can be expressed as a general equation as were the acids in the previous section. The equations for the bases are:

$$R_r = \prod_{\pi=0}^r KR_{\pi} H^{-r} R_0 \quad (\text{Eq. 42})$$

and:

$$S_s = \prod_{\pi=0}^s KS_{\pi} H^{-s} S_0 \quad (\text{Eq. 43})$$

A general equation for a system of two polyacidic bases can be derived in a manner analogous to Eq. 31 for the system of two polybasic acids. The equation thus derived is:

$$DK_{rs}H_{rs} = K_{r's}H_{r's}TR + K_{rs'}H_{rs'}TS \quad (\text{Eq. 44a})$$

where  $K_{r's} = K_{rs}(r - NR)$  and  $K_{rs'} = K_{rs}(s - NS)$ .

The derivation of Eq. 44a can be extended to a system of any number of bases analogous to the extension of Eq. 31 to Eq. 32. The general equation for any number of polyacidic bases is:

$$DK_{rs\dots z}H_{rs\dots z} = K_{r's\dots z}H_{r's\dots z}TR + K_{rs'\dots z}H_{rs'\dots z}TS + \dots + K_{rs\dots z'}H_{rs\dots z'}TZ \quad (\text{Eq. 44b})$$

**Mixture of Weak Acids, Weak Bases, Ampholytes, Salts, and Strong Bases**—Inspection of Eqs. 31 and 44a reveals a mathematical similarity. If an  $NP$  term and an  $NQ$  term had been defined for the acids, as  $NR$  and  $NS$  were defined for the bases, then the equations would have been mathematically identical ( $NP$  and  $NQ$  would have been zero since no cationic species of the acids were formed). Therefore, Eq. 44a can be applied to mixtures of acids, mixtures of bases, and mixtures of acids and bases.

Equation 44a also is applicable to ampholytes, but caution must be exercised in the determination of the number of cationic species possible.

Salts can be considered as mixtures of acids and bases. Therefore, Eq. 44a is applicable to solutions formed from salts. Mathematically, the solution is considered to be formed from a stoichiometric mixture of the acid and base components of the salt.

The addition of a strong acid and/or strong base to any mixture requires modification of the charge balance. Let  $SB_t$  denote the total concentration of strong base and  $SA_t$  denote the total concentration of strong acid. If one component of a salt is a strong acid or base, then its concentration must be added to the  $SA_t$  or  $SB_t$  term, respectively.

*Example 1: Ammonium Acetate*—This salt is treated as an equimolar mixture of ammonia ( $TP$ ) and acetic acid ( $TQ$ ):  $TP = TQ$ ,  $NP = 1$ , and  $NQ = 0$ .

*Example 2: Sodium Acetate*—This salt is treated as an equimolar mixture of acetic acid ( $TP$ ) and sodium hydroxide ( $SB_p$ ):  $TP = SB_t$ ,  $NP = 0$ , and  $SB_t = SB_p$ .

*Example 3: Sodium Carbonate*—This salt is treated as a mixture of sodium hydroxide ( $SB_p$ ) and carbonic acid ( $TP$ ):  $2TP = SB_p$ ,  $NP = 0$ ,  $SB_t = SB_p$ .

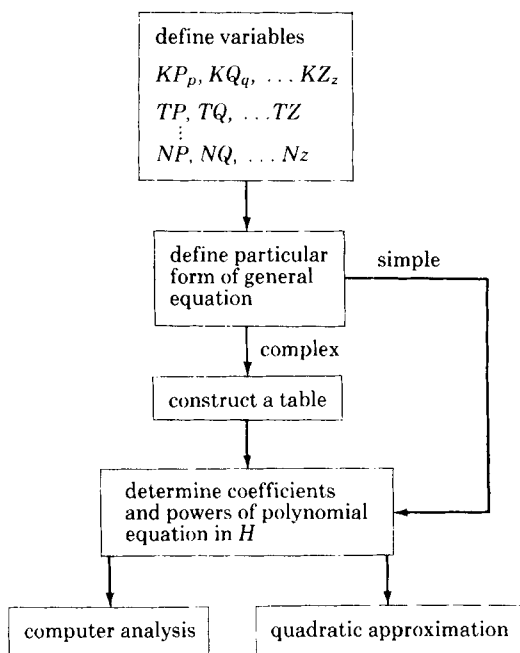
*Example 4: Sodium Carbonate and Sodium Hydroxide*—This solution is treated as a mixture of carbonic acid ( $CP$ ) and sodium hydroxide as in Example 3; however, the additional sodium hydroxide is added to the  $SB_t$  term:  $2TP = SB_p$ ,  $NP = 0$ , and  $SB_t = SB_p + SB$ .

Therefore, Eq. 44b can be extended to mixtures of weak acids, weak bases, ampholytes, salts, strong acids, strong bases, and all of their combinations. The general equation (derived analogously to Eq. 44b) is:

$$(SB_t - SA_t + D)K_{pq\dots z}H_{pq\dots z} = K_{p'q\dots z}H_{p'q\dots z}TP + K_{pq\dots z'}H_{pq\dots z'}TQ + K_{pq\dots z}H_{pq\dots z}TZ \quad (\text{Eq. 44c})$$

## GENERAL METHOD AND APPLICATION

The substitution of known values into Eq. 44b for a particular mixture followed by rearrangement and collection of terms in  $H$  results in a



Scheme XIII

polynomial in  $H$ . The determination of the coefficients and the order of the polynomial can be facilitated by constructing a table for the systematic enumeration of: (a) all possible values of the subscripts of the tensor  $K_{pq...z}$ , (b) the powers of the polynomial in  $H$  that correspond to the subscripts, (c) the values of the components of  $K_{pq...z}$ , and (d) the stoichiometric factors for each component.

The table also allows a numerical comparison of the contribution of each term to a particular coefficient. This comparison permits omission of insignificant terms. The advantage of this method increases with the complexity of the mixture.

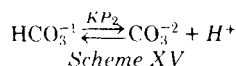
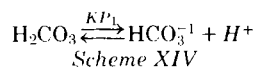
The final polynomial in  $H$  obtained from the table can be solved by numerous numerical computer techniques. However, a quadratic approximation of the polynomial also can be used (1), eliminating the need of a computer.

The general procedure to calculate the hydrogen-ion concentration of a complex system is illustrated in Scheme XIII. A step-by-step approach of the general procedure with specific application to a simple and a complex mixture follows.

Consider the calculation of the hydrogen-ion concentration in a solution of 0.09  $M$   $\text{NaHCO}_3$  and 0.01  $M$   $\text{Na}_2\text{CO}_3$ :

1. The number of actual components is specified. This particular mixture contains two, carbonic acid and sodium hydroxide (refer to previous section).

2. The ionization constants for each component (excluding strong acids and strong bases) are defined. The total number of ionizations for each component also is defined ( $\alpha, \beta, \dots, \omega$ ). The values for this example are:  $K_{P1} = 4.20E-07$  for the equilibrium shown in Scheme XIV and  $K_{P2} = 4.80E-11$  for the equilibrium shown in Scheme XV, with  $\alpha = 2$ .



3. The number of cationic species formed from each actual component (excluding strong acids and strong bases) is determined. The only component to be considered in this example is carbonic acid, which does not form any cationic species. Therefore, the  $NP$  term is equal to zero.

4. The total concentration of each component is determined. The components for this example are carbonic acid and sodium hydroxide. The mass balance for the sodium hydroxide is:  $SB_t = 0.09 M + 2(0.01 M) = 0.11 M$  (sodium hydroxide). The mass balance for the carbonic acid is:  $TP = 0.09 M + 0.01 M = 0.1 M$  (carbonic acid).

5. By using the general equation (Eq. 44c), a particular (general) equation for the mixture is defined. The equation for this example is:

$$(I + SB_t)K_p H_p = PK_p H_p \quad (\text{Eq. 45})$$

Table I—Data for Example 1

$p$	$H^n$	$p - NP$ ( $CP = 1.00E-01M$ )	$K_p$ ( $SB_t = 1.10E-01M$ )
0	2	0	1
1	1	1	$4.20E-07$
2	0	2	$2.00E-17$

6. The known values (Steps 1–4) are substituted into the equation obtained from Step 5. If the equation is simple, then a direct substitution can be performed after expansion of the equation. Expanding Eq. 45 yields:

$$(I + SB_t)(H^2 + KP_1H + KP_1KP_2) = (KP_1H + 2KP_1KP_2)P \quad (\text{Eq. 46})$$

Substituting the values from Steps 1–5 and Eq. 15b into Eq. 46 yields the final equation for this example:

$$H^4 + (1.1E-01)H^3 + (4.2E-09)H^2 - (1.8E-18)H - 2.01E-31 = 0 \quad (\text{Eq. 47})$$

In more complex situations, rearranging Eq. 45 or whatever general equation results from Step 5 results in a more useful form for substitution of the variables:

$$DK_p H_p + SB_t K_p H_p - PK_p H_p = 0 \quad (\text{Eq. 48})$$

A table can be constructed that allows the evaluation of the coefficients of Eq. 48 without expanding the general equation. The table is constructed in the following manner (Table I):

a. A column is constructed that contains each possible combination of  $p, q, \dots, z$ . The total number of rows (combinations) equals  $(\alpha + 1)(\beta + 1) \dots (\omega + 1)$ . In Table I, the three values possible for  $p$  in this example are shown in the first column.

b. With the values obtained in the first column, a second column is calculated. This column contains the relative powers of  $H$  in the final polynomial. The power is calculated for each row in the second column by using the value of the subscripts  $p, q, \dots, z$  in the corresponding row of the first column and solving:

$$(\alpha + \beta + \dots + \omega) - (p + q + \dots + z) = \text{power of } H \quad (\text{Eq. 49})$$

c. A column for each component (excluding strong acids and strong bases) is constructed. In Table I, only one column for component  $CP$  (carbonic acid) is required for this example. In general, the rows of the component columns are determined from the corresponding entries in the first column and by calculating  $p - NP, q - NQ, \dots, z - NZ$ . Since  $NP$  is zero, the component column is equivalent to the first column for this example.

d. The last column is constructed by calculating  $K_{pq...z}$  from the corresponding values of the subscripts  $p, q, \dots, z$  in the first column. The nature of the  $K_{pq...z}$  tensor allows each succeeding row after the first to be calculated from a previous row (not necessarily the last row) by multiplication with the next ionization constant corresponding to the new subscript. This column is labeled  $K_{pq...z}$  and subtitled with the appropriate concentration of  $SB_t - SA_t$ . The resultant column for this example is shown in Table I.

7. The next step is to calculate the coefficients and powers of the final polynomial equation. Starting with the highest power of  $H$ , the entry is determined under each component for the row corresponding to that power. The value obtained is multiplied by the component concentration ( $s$ ). This value is subtracted from the  $SB_t - SA_t$  concentration. The difference obtained then is multiplied by the corresponding value in the  $K_{pq...z}$  column and by the corresponding value of  $H^n$ . (In more complex systems, more than one row will be found for a given order. If the values for rows of a given power are equal in magnitude, they are added. If the values are not equal, then the minor contributing row may be ignored.) This procedure is repeated for each decreasing power of  $H$ . The values for each power then are added. The values for this example are: power 2 =  $(1.10E-01)(1)H^2$ , power 1 =  $(1.10E-01 - 1.00E-01)(4.20E-07)H^1$ , and power 0 =  $(1.10E-01 - 2.00E-01)(2.01E-17)H^0$ , so that:

$$\Sigma = (1.10E-01)H^2 + (4.20E-09)H^1 - (1.81E-18)H^0 \quad (\text{Eq. 50})$$

The summation obtained in general will equal the total equation (Eq. 48 for this example) minus the term  $DK_{pq...z}H_{pq...z}(DK_p H_p$  for this example). This term can be expanded after substituting Eq. 15b to yield:

Table II—Data for Example 2

	<i>p</i>	<i>q</i>	<i>r</i>	<i>s</i>	<i>H<sup>n</sup></i>	<i>p</i> - NP TP 2.16E-02	<i>q</i> - NQ TQ 2.16E-02	<i>r</i> - NR TR 2.16E-02	<i>s</i> - NS TS 2.16E-02	<i>K<sub>pqrs</sub></i> SB <sub>i</sub> 7.07E-02
*a	0	0	0	0	8	0	0	0	0	1
	0	0	1	0	7	0	0	0	1	5.80E-10
	0	0	1	0	7	0	0	1	0	3.70E-08
	0	0	1	1	6	0	0	1	1	2.15E-17
*	0	1	0	0	7	0	1	0	0	7.50E-03
	0	1	0	1	6	0	1	0	1	4.35E-12
	0	1	1	0	6	0	1	1	1	2.78E-10
	0	1	1	1	5	0	1	1	1	1.61E-19
	0	2	0	0	6	0	2	0	0	4.65E-10
	0	2	0	1	5	0	2	0	1	2.69E-19
	0	2	1	0	5	0	2	1	0	1.72E-17
	0	2	1	1	4	0	2	1	1	9.98E-27
	0	3	0	0	5	0	3	0	0	2.23E-22
	0	3	0	1	4	0	3	0	1	1.29E-31
	0	3	1	0	4	0	3	1	0	8.25E-30
	0	3	1	1	3	0	3	1	1	4.79E-39
*	1	0	0	0	7	1	0	0	0	8.40E-04
	1	0	0	1	6	1	0	0	1	4.82E-13
	1	0	1	0	6	1	0	1	0	3.11E-11
	1	0	1	1	5	1	0	1	1	1.80E-20
*	1	1	0	0	6	1	1	0	0	6.30E-06
	1	1	0	1	5	1	1	0	1	3.65E-15
	1	1	1	0	5	1	1	1	0	2.33E-13
	1	1	1	1	4	1	1	1	1	1.35E-22
	1	2	0	0	5	1	2	0	0	3.91E-13
	1	2	0	1	4	1	2	0	1	2.27E-22
	1	2	1	0	4	1	2	1	0	1.45E-20
	1	2	1	1	3	1	2	1	1	8.41E-30
	1	3	0	0	4	1	3	0	0	1.89E-25
	1	3	0	1	3	1	3	0	1	1.10E-34
	1	3	1	0	3	1	3	1	0	6.99E-33
*	1	3	1	1	2	1	3	1	1	4.05E-42
*	2	0	0	0	6	2	0	0	0	1.50E-08
	2	0	0	1	5	2	0	0	1	8.70E-18
	2	0	1	0	5	2	0	1	0	5.55E-16
	2	0	1	1	4	2	0	1	1	3.22E-25
*	2	1	0	0	5	2	1	0	0	1.13E-10
	2	1	0	1	4	2	1	0	1	6.57E-20
*	2	1	1	0	4	2	1	1	0	4.19E-18
	2	1	1	1	3	2	1	1	1	2.43E-27
*	2	2	0	0	4	2	2	0	0	7.04E-18
	2	2	0	1	3	2	2	0	1	4.09E-27
*	2	2	1	0	3	2	2	1	0	2.61E-25
	2	2	1	1	2	2	2	1	1	1.51E-34
	2	3	0	0	3	2	3	0	0	3.40E-30
	2	3	0	1	2	2	3	0	1	1.98E-39
	2	3	1	0	2	2	3	1	0	1.26E-37
	2	3	1	1	2	2	3	1	1	7.29E-47
	3	0	0	0	5	3	0	0	0	6.00E-14
	3	0	0	1	4	3	0	0	1	3.48E-23
	3	0	1	0	4	3	0	1	0	2.22E-21
*	3	0	1	1	3	3	0	1	1	1.29E-29
	3	1	0	0	4	3	1	0	0	4.52E-16
	3	1	0	1	3	3	1	0	1	2.63E-25
*	3	1	1	0	3	3	1	1	0	1.68E-23
	3	1	1	1	2	3	1	1	1	9.72E-33
*	3	2	0	0	3	3	2	0	0	2.82E-23
*	3	2	0	1	2	3	2	0	1	1.64E-32
*	3	2	1	0	2	3	2	1	0	2.04E-30
*	3	2	1	1	1	3	2	1	1	6.04E-40
	3	3	0	0	2	3	3	0	0	1.36E-35
	3	3	0	1	1	3	3	0	1	7.92E-45
	3	3	1	0	1	3	3	1	0	5.04E-43
*	3	3	1	1	0	3	3	1	1	2.92E-52

\* The asterisk indicates the row contributing significantly to the total Eq. 55.

$$\left(\frac{H^2 - K_w}{H}\right) K_{pq...z} H_{pq...z} \quad (\text{Eq. 51})$$

The  $K_{pq...z} H_{pq...z}$  value is computed using the table by recalling the rows used in the determination of the coefficients of the polynomial. Since all three rows were used in this example:

$$K_p H_p = H^2 + (4.20E-07)H^1 + (2.01E-17)H^0 \quad (\text{Eq. 52})$$

The final equation can be obtained by substituting the values obtained from the summation, the  $K_{pq...z} H_{pq...z}$  value, and Eq. 15b into the general equation. The result for this example is obtained by substituting Eqs. 50, 52, and 15b into Eq. 48 to yield:

$$H^4 + (1.10E-01)H^3 + (4.20E-09)H^2 - (1.81E-18)H^1 - (2.01E-31)H^0 = 0 \quad (\text{Eq. 53})$$

8. The last step is the numerical solution of the final equation. For this example, Eq. 53 can be solved by numerical techniques. However, the quadratic equation obtained from the last three terms of Eq. 53 approximates the total equation. This approximation yields a pH of 9.37, the same as that given by Eq. 53 to this accuracy. Experimentally, a pH of 9.30 was obtained.

The second example is the calculation of the hydrogen-ion concentration of a solution of 0.0216 M citric acid (P), 0.0216 M monobasic sodium phosphate (Q), 0.0216 M barbital (R), 0.0216 M boric acid (S), and

0.0491 M NaOH, which can be solved as follows:

1. There are five components of this mixture: citric acid, phosphoric acid, barbital, boric acid, and sodium hydroxide.

2. The ionization constants,  $\alpha$ ,  $\beta$ ,  $\gamma$ , and  $\delta$ , for this example are defined as:  $KP_1 = 8.40E-04$ ,  $KQ_1 = 7.50E-03$ ,  $KS_1 = 5.80E-10$ ,  $KP_2 = 1.80E-05$ ,  $KQ_2 = 6.20E-08$ ,  $KR_1 = 3.70E-08$ ,  $KP_3 = 4.00E-06$ ,  $KQ_3 = 4.80E-13$ ,  $\alpha = 3$ ,  $\beta = 3$ ,  $\gamma = 1$ , and  $\delta = 1$ .

3. There are no cationic species formed from any of the components. Therefore,  $NP = NQ = NR = NS = 0$ .

4. The component concentrations are:  $TP = TQ = TR = TS = 0.0216 M$  and  $SB_t = 0.0491 M$  (sodium hydroxide) +  $0.0216 M$  ( $SB_q$ ) =  $0.0707 M$ .

5. The general equation for this particular mixture is then defined from Eq. 44c. Equation 44c for a mixture of four components ( $TP$ ,  $TQ$ ,  $TR$ , and  $TS$ ) and  $SB_t$  results in:

$$(D + SB_t)K_{pqrs}H_{pqrs} = K_{p'qrs}H_{p'qrs}TP + K_{pq'r's}H_{pq'r's}TQ + K_{pqr's}H_{pqr's}TR + K_{pqrs'}H_{pqrs'}TS \quad (\text{Eq. 54})$$

6. The tableau method for the calculation of coefficients and powers in the final polynomial is advantageous for this example because of its complexity. Rearranging Eq. 54 and substituting Eq. 15b yield:

$$\left(\frac{H^2 - K_w}{H}\right)K_{pqrs}H_{pqrs} = (SB_tK_{pqrs} - TPK_{p'qrs} - TQK_{pq'r's} - TRK_{pqr's} - TSK_{pqrs'})H_{pqrs} \quad (\text{Eq. 55})$$

Table II was constructed using the procedure outlined in the previous example. However, in this example, not every row was used in calculating the coefficients. Only 16 rows contributed significantly to the total equation. The values in the  $K_{pqrs}$  column for a given power should be compared and the relative values noted. These contributing rows are marked with an asterisk in Table II.

7. The coefficients for each power are determined from Step 6 and summed for all powers of  $H$ . This sum equals the right side of Eq. 55. The value of  $K_{pqrs}H_{pqrs}$  is calculated by recalling all of the contributing rows used in the determination of the previous summation. The values in the  $K_{pqrs}H_{pqrs}$  column corresponding to these rows are added. Substituting the value obtained for the right side of Eq. 55 and the value obtained for  $K_{pqrs}H_{pqrs}$  into Eq. 55 and expanding yield the final equation for this system:

$$H^{10} + (7.9E-02)H^9 + (4.2E-04)H^8 + (1.7E-07)H^7 + (6.7E-13)H^6 - (7.3E-18)H^5 - (1.72E-24)H^4 - (6.2E-32)H^3 - (4.9E-41)H^2 - (3.6E-53)H^1 - (2.9E-66)H^0 = 0 \quad (\text{Eq. 56})$$

8. This step is performed as in the previous example. The quadratic

approximation based on  $H^7$  yields a pH of 5.37, whereas solving the entire Eq. 55 gives a pH of 5.30. The latter pH was the one obtained experimentally.

## EXPERIMENTAL

The pH measurements were performed using a digital pH meter<sup>1</sup>. The instrument and test solutions were at 23°. Buffer solutions bracketing the approximate pH of the test solution were used to calibrate the instrument.

## RESULTS AND DISCUSSION

The results for two- and five-component mixtures of acids, bases, and ampholytes showed reasonable agreement between experimental and calculated pH values. The general method presented has the advantage that approximations can be made in the final equation rather than in the derivation. This approach allows the approximation to be based on numerical comparison rather than on intuition. Additionally, the method can be used without any approximation if a computer is available (the general nature of the final equation is well suited for computer analysis). In summary, the general equation presented is simple and versatile; it can be used to calculate the hydrogen-ion concentration of simple and complex solutions. However, at high ionic strengths, the lack of activity corrections is expected to limit the accuracy of the method.

## REFERENCES

- (1) J. E. Ricci, "Hydrogen Ion Concentration," Princeton University Press, Princeton, N.J., 1952, pp. i-v, 121-136.
- (2) I. G. Sillen, in "Treatise on Analytical Chemistry," part I, vol. 2, Interscience, New York, N.Y., 1959.
- (3) H. Jeffreys, "Cartesian Tensors," Cambridge University Press, London, England, 1963, pp. 2-4.

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<sup>1</sup> Ionalyzer model 807, Orion Research.