Structure–Neuromuscular Blocking Activity Relationships of Ketophosphonium Salts

RAYMOND HOUSSIN [x], **JEAN-PIERRE HÉNICHART** *, **MICHEL FOULON** [‡], **and FRANÇOIS BAERT** [‡]

Received October 4, 1979, from the *Institut de Chimie Pharmaceutique, Université de Lille II, rue du Professeur Laguesse, 59045 Lille, France.* Accepted for publication February 26, 1980. *INSERM U16, Place de Verdun, 59045 Lille, France. [‡]Laboratoire de Dynamique des Cristaux Moléculaires, ERA 465, 59650 Villeneuve d'Ascq, France.

Abstract □ Three ketophosphonium salts containing a morpholino group were prepared and evaluated for their neuromuscular blocking effect. Solution and crystal conformations were studied. An attempt was made to explain, in structural terms, different activity levels in connection with the interatomic distances.

Keyphrases □ Ketophosphonium salts—synthesis, relationship between neuromuscular blocking activity and interatomic distances □ Structure–activity relationships—ketophosphonium salts, relationship between neuromuscular blocking activity and interatomic distances □ Neuromuscular blocking activity—ketophosphonium salts, relationship between activity and interatomic distances

The striking relationship between neuromuscular blocking potency and chain length (1–3) or spatial configuration (4–6) in a series of bis-onium salts has been recognized. Replacement of the ammonium moiety by sulfonium, arsonium, or stilbonium has been studied, but the change of one of the two electropositive sites for a phosphonium group has not been well documented (7, 8).

To determine whether it could alter such activity, a triphenylphosphonium salt was introduced on an aliphatic chain with two polar groups. These derivatives exhibit a blocking effect, and the geometric characteristics of the molecules in the crystalline state and in solution were studied to correlate their structure with their biological activity. Their conformations were studied by PMR in solution and by X-ray diffraction in the solid state, enabling evaluation of the distance between the two cations.

EXPERIMENTAL

Methods—Melting points were determined in open glass capillaries and are uncorrected. IR[1] spectra were taken on a double-beam spectrophotometer, utilizing a potassium bromide pellet for solid samples and sodium chloride windows for liquids. PMR[2] spectra were recorded on a 60-MHz instrument. Accurate cell parameters were determined on an automatic diffractometer[3] using Mo K_α radiation. Intensity data also were collected on this instrument.

The structures were solved by direct methods using the Multan program (9). The atoms were normally located by direct and difference Fourier maps, except for some hydrogen atoms. The functional analysis was carried out with the determination of the mean planes and intramolecular distances. Analytical results[4] for the elements were within ±0.4% of theoretical values.

Syntheses—*4-Morpholino-2-butanone (I)*—Concentrated hydrochloric acid (50 ml, 0.5 mole) was added dropwise to a stirred suspension of *s*-trioxane (22.2 g, 0.75 mole) in a cold mixture (5°) of morpholine (43.5 g, 0.5 mole), acetone (200 ml, 2.7 moles), and methanol (30 ml). The mixture was refluxed for 12 hr, cooled, and evaporated to dryness *in vacuo*. A solution of the residue in water (50 ml) was made slightly basic with 10% NaOH and extracted with ether; the combined ethereal solutions were dried over sodium sulfate, evaporated, and distilled under reduced pressure to give 63 g (83% yield) of a colorless liquid, bp 68–74° (0.01 mm).

1-Bromo-4-morpholino-2-butanone Hydrobromide (II)—A solution of bromine (5.1 ml, 0.1 mole) in acetic acid (6 ml) was added dropwise at room temperature to a solution of I (15.7 g, 0.1 mole) in a mixture of hydrobromic acid (20 ml, 0.3 mole) and acetic acid (25 ml). The resulting solution was heated at 40° for 2 hr and then evaporated; crystallization occurred after trituration of the pasty residue with ethanol. Recrystallization from ethanol gave 23.8 g (75% yield) of II, mp 179°.

Anal.—Calc. for $C_8H_{15}Br_2NO_2$: C, 30.31; H, 4.77; N, 4.42. Found: C, 30.39; H, 4.73; N, 4.44.

(2-Oxo-4-morpholino)butyltriphenylphosphonium Bromide Hydrobromide (III)—A mixture of 31.7 g (0.1 mole) of II and 26.2 g (0.1 mole) of triphenylphosphine in 100 ml of anhydrous chloroform was heated to reflux for 12 hr under nitrogen. The solvent was evaporated, and the residue was triturated with an anhydrous ethanol–ether mixture. The resulting solid was recrystallized from ethanol to give 37 g (65% yield) of III, mp 209°.

Anal.—Calc. for $C_{26}H_{30}Br_2NO_2P$: C, 53.91; H, 5.22; N, 2.42. Found: C, 53.61; H, 5.21; N, 2.59.

(2-Oxo-3-chloro)propyltriphenylphosphonium Chloride (IV)—A mixture of 1,3-dichloroacetone (2.5 g, 0.02 mole) and triphenylphosphine (5.2 g, 0.02 mole) in benzene was heated under reflux for 2 hr. The precipitate was collected and crystallized from 95% ethanol to yield 6.9 g (85% yield) of IV·H_2O, mp 173°.

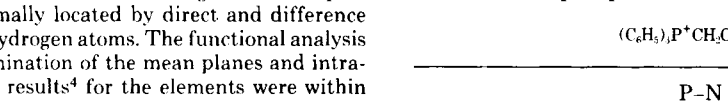
Anal.—Calc. for $C_{21}H_{19}Cl_2OP \cdot H_2O$: C, 61.93; H, 5.20. Found: C, 62.04; H, 5.25.

(2-Oxo-3-morpholino)propyltriphenylphosphonium Chloride Hydrochloride (V)—To a solution of IV (4.1 g, 0.01 mole) and morpholine hydrochloride (1.2 g, 0.01 mole) was added sodium (0.7 g, 0.03 mole) in ethanol. The reaction mixture was refluxed for 3 hr. Sodium chloride was filtered, and ethanolic hydrochloric acid was added to the filtrate. After evaporation of the solvent, the crude product was recrystallized from ethanol to yield 3.5 g (74% yield) of V, mp 165°.

Anal.—Calc. for $C_{25}H_{28}Cl_2NO_2P$: C, 63.03; H, 5.92; N, 2.94. Found: C, 62.92; H, 5.80; N, 2.87.

N-(Chloroacetyl)morpholine (VI) (10)—To a cold solution (−10°) containing 13 g (0.15 mole) of morpholine in a mixture of ethylene dichloride (50 ml) and 20% NaOH (20 ml) was added dropwise 11.3 g (0.1 mole) of chloroacetyl chloride. After stirring at 20° for 1 hr, the reaction mixture was left at 5° overnight. The organic layer was separated, and the aqueous phase was extracted with ethylene dichloride. The organic extracts were washed (10% HCl, 5% $NaHCO_3$, and water), dried (sodium

Table I—Ketophosphonium Salts



Compound	*n*	X	P–N Distance, Å	Dose, mg/kg ED_{50}[a]	BP[b]	RA[c]	LD_{50}
III[d]	2	Br	6.48	55 ± 1.9	20	55	107 ± 3
V[e]	1	Cl	5.51	84 ± 3.0	50	80	210 ± 5
VII	0	Cl	3.91	25 ± 0.8	40	26	220 ± 3
Gallamine triethiodide				3.5 ± 0.1	4	4	

[a] The ED_{50} values are doses estimated ($p < 0.01$) to decrease the amplitude of the action potential by 50%. [b] The BP values are doses inducing a significant decrease in blood pressure. [c] Doses corresponding to a respiratory arrest. [d] Hydrobromide. [e] Hydrochloride.

[1] Perkin-Elmer 177 spectrometer.
[2] Jeol JNM-MH-60 instrument.
[3] Philips PW 1100.
[4] Perkin-Elmer 240 carbon, hydrogen, and nitrogen analyzer.

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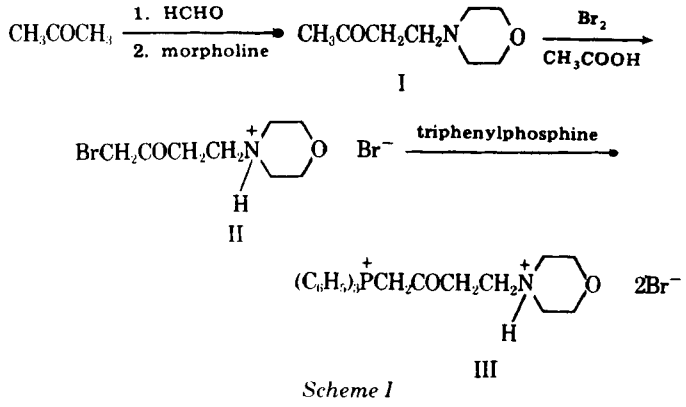


Scheme I

sulfate), and concentrated *in vacuo*. Distillation afforded 12 g (73% yield) of VI, bp 106° (0.01 mm).

(2-Oxo-2-morpholino)ethyltriphenylphosphonium Chloride (VII)—A solution of 16.3 g (0.1 mole) of VI and 26.2 g (0.1 mole) of triphenylphosphine in dry benzene (50 ml) was refluxed for 5 hr under nitrogen. The hot mixture was filtered, and the precipitate was washed with anhydrous ether. Recrystallization from isopropanol yielded 30.6 g (72% yield) of VII, mp 225°; IR (KBr): 1630 (C=O) cm^{-1}; PMR (acetonitrile-d_3): δ 3.47 (m, 4H, CH_2NCH_2), 3.72 (s, 4H, CH_2OCH_2), 5.71 (d, 2H, P^+CH_2, $J_{P,H}$ = 13 Hz), and 7.73 (m, 15H, phenyl).

Anal.—Calc. for $C_{24}H_{25}ClNO_2P$: C, 67.68; H, 5.92; N, 3.29. Found: C, 67.35; H, 6.01; N, 3.34.

(2-Oxo-4-morpholino)butyltriphenylphosphorane (IIIc)—A 10% K_2CO_3 solution (25 ml, 0.017 mole) was added slowly to III (5.8 g, 0.01 mole) dissolved in a minimum of water in a nitrogen atmosphere at 20°. The crude precipitate was filtered after 2 hr and recrystallized from ethyl acetate to afford 3.7 g (88% yield) of IIIc, mp 135°.

Anal.—Calc. for $C_{26}H_{28}NO_2P$: C, 74.81; H, 6.76; N, 3.36. Found: C, 74.70; H, 6.60; N, 3.29.

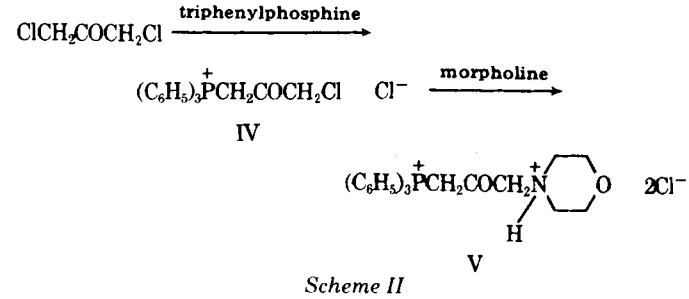
Pharmacology—*Neuromuscular Blocking Potency*—The gastrocnemius muscle-sciatic nerve preparation was obtained from anesthetized rats (average weight 350 g) by intravenous injection of 0.4 ml of 6% pentobarbital sodium[5]. Contractions were produced by stimulating the nerve within the muscle at a frequency of 1 Hz with rectangular pulses of 1 msec in duration and 30 mv in amplitude and were recorded together with the arterial blood pressure. Animals were placed under artificial respiration.

Tested drugs were compared with gallamine triethiodide[6], with the effects being considered equal when a test concentration produced a 50% inhibition of the action potential (ED_{50}).

LD_{50} Determination—The acute, single-dose toxicity of III, V, and VII in mice following intraperitoneal administration is shown in Table I in terms of the quantitative lethal potency determined by the Miller and Tainter method (11).

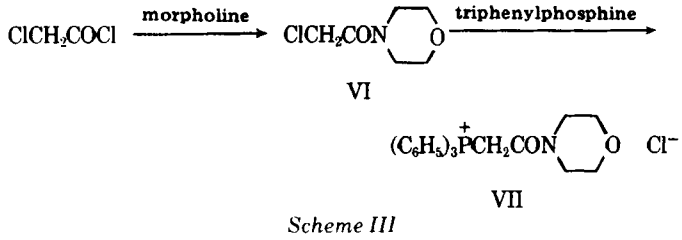
RESULTS

Chemistry and Spectral Studies—Schemes I–III illustrate the syntheses of the phosphonium salts. 4-Morpholino-2-butanone (I) was prepared from acetone *via* the Mannich reaction as described previously (12). The corresponding 1-bromo derivative (the hydrobromide salt, II) subsequently was obtained in a good yield from the acetic acid-catalyzed



Scheme II

[5] Nembutal, Abbott, Levallois, France.
[6] Flaxedil, Specia, Paris, France.



Scheme III

bromination. Direct substitution of II with 1 equivalent of triphenylphosphine in anhydrous chloroform under an inert atmosphere yielded the phosphonium salt (III).

Preparation of (2-oxo-3-morpholino)propyltriphenylphosphonium chloride hydrochloride (V) was achieved by reacting 1,3-dichloroacetone with triphenylphosphine, yielding IV, which then was converted into V with morpholine. Treatment of chloroacetyl chloride with morpholine afforded the amide (VI), and further condensation with triphenylphosphine gave (2-oxo-2-morpholino)ethyltriphenylphosphonium chloride (VII).

The structures of V and VII in the solid state as well as in solution require no special discussion; examination of the X-ray diffraction data and the NMR spectra confirmed the observations revealed by IR spectroscopy, which evidenced their ketonic and amide functions, respectively.

Compound III demands more precise investigation. An X-ray diffraction analysis (Figs. 1 and 2) indicated that the molecule shows an expanded position, probably due to better, stronger packing. Phosphonium and ketone groups are *gauche* with respect to the C_1–C_2 bond, and the C=O does not deviate far from the P–C_1–C_2 plane. The electronic perturbations found here and, in particular, the effect of an α-carbonyl group on the length of the P–C_1 bond confirm previous studies about alkyltriphenylphosphonium salts (13–27). Moreover, the presence of a morpholinyl nitrogen, protonated or not, is apt to bring modifications in the geometry of the PC_1C_2O moiety and to induce a preferential conformation for III in solution. Evidence that III is a mixture of the keto and enol species (Scheme IV) with predominance of the former is given by the presence in the IR spectrum (Table II) of two absorptions at 1720 and 1615 cm^{-1}, the latter being assigned to the C=C stretching of an enolic function. The establishment of the III⇌IIIa equilibrium is confirmed further by the PMR spectral data, which, when obtained in a chloroform medium, included a singlet at a lower field attributable to the hydroxyl hydrogen.

Because the structure of IIIa may give rise to possible *cis–trans* isomers (22), the related phosphorane (IIIc), which presents the same particu-

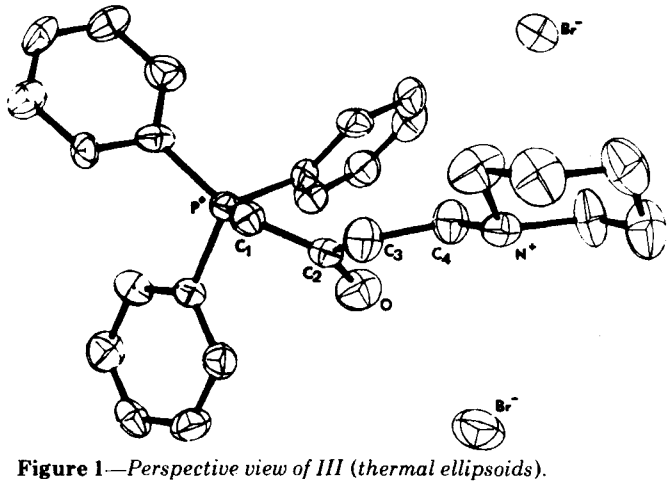


Figure 1—*Perspective view of III (thermal ellipsoids).*

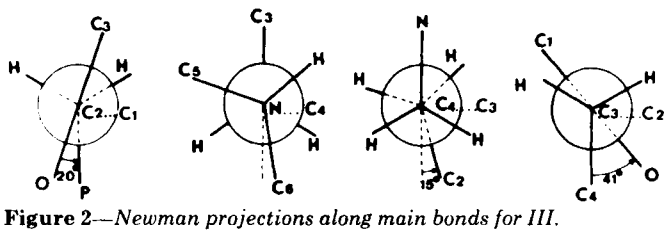
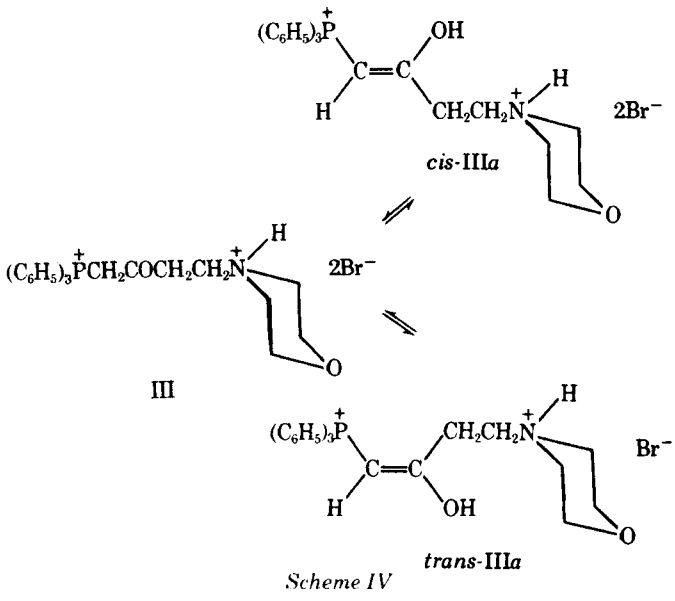


Figure 2—*Newman projections along main bonds for III.*

Table II—PMR and IR Data for III, III*a*, and III*c*

Compound	PMR[a], δ a	b	c	d	e	f	g	Phenyl	IR, cm^{-1}
$(C_6H_5)_3P^+CH_2COCH_2CH_2N$ (O) $2Br^-$	6.10[b] (d, 2)		3.58 (m, 8)		4.03 (m, 4)	10.50 (m, 1)		7.85 (m, 15)	$\nu_{C=O}$ = 1720 (KBr)
$(C_6H_5)_3P^+CH=CCH_2CH_2N$ (O) $2Br^-$	4.25[c] (d, 1)		3.58 (m, 8)		4.03 (m, 4)	10.50 (m, 1)	12.80 (s, 1)	7.85 (m, 15)	$\nu_{C=C}$ = 1615 ($CHCl_3$) ν_{OH} = 3400 ($CHCl_3$)
$(C_6H_5)_3P^+CH-CCH_2CH_2N$ (O)	3.75[d] (d, 1)		2.65[e] (m, 8)		3.70 (m, 4)			7.58 (m, 15)	ν_{C-O} = 1550 (KBr)

[a] PMR spectra were run in deuterochloroform; chemical shifts are expressed in parts per million relative to tetramethylsilane; s = singlet, d = doublet, and m = multiplet. [b] $^2J_{P,H}$ = 12 Hz. [c] $^2J_{P,H}$ = 19.5 Hz. [d] $^2J_{P,H}$ = 26.2 Hz. [e] $^3J_{b,c}$ = 6 Hz.

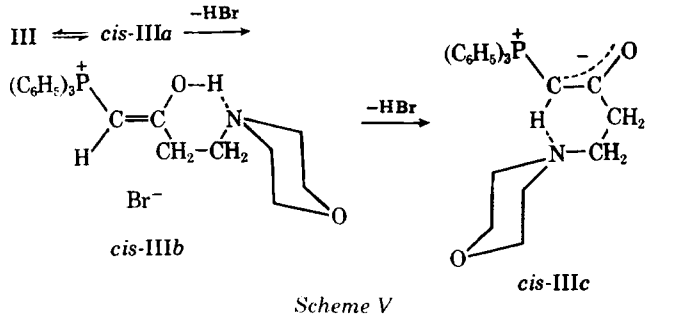


Scheme IV

larity, was studied; its geometry is easier to establish and allows the determination of the respective positions of phosphorus and oxygen in the parent compound (III*a*).

The phosphorane (III*c*) was obtained by addition of a basic reagent in a calculated amount. A first dehydrohalogenation led to the phosphonium bromide (III*b*), whose enolic form is stabilized by hydrogen bonding; its stereochemistry cannot be ascertained from routine experiments. However, further dehydrohalogenation gave the phosphorane (III*c*), and IR data (28–36) revealed the presence of only one rotation isomer (*cis*-III*c*) with the cyclic enolic structure strongly favored by the P^+O^- interaction and by the H···N hydrogen bonding (Scheme V). This latter bonding (37) is confirmed by the dihedral angle ($0 < \alpha < 30°$) determined from $^3J_{b,c}$ = 6 Hz (38–40). Furthermore, the rotation about the C_1–C_2 double bond was observed by NMR at 48° in chloroform, but this phenomenon did not occur up to 150° in dimethyl sulfoxide.

The *cis*-structure of III*c* suggests that its precursor (III*a*) presents the



Scheme V

Table III—Crystal Data for III

Formula	$C_{26}H_{30}Br_2NO_2P$
Mol. wt.	579.323
Space group	$P\bar{1}$
a	12.73 (2) Å
b	12.79 (2) Å
c	9.66 (1) Å
α	115°80
β	105°12
γ	66°53
V	1292 $Å^3$
$d_{calc.}$	1.43 g/cm^3
Z	2
Unit cell	Triclinic
R	0.071 (2396 strongest structure factors)
μ	30 cm^{-1}

same configuration in solution and thereby renders the *gauche*-conformation more likely (at the dihedral PC_1C_2O site) for the corresponding ketonic form (III) in solution, as proved by X-ray diffraction (Figs. 1 and 2 and Table III).

Biological Testing—The neuromuscular blocking potencies were tested on the gastrocnemius muscle–sciatic nerve preparation of the anesthetized rat and compared with effects of gallamine triethiodide. The results in Table I are expressed in terms of variations in the amplitude of the action potential. Arterial blood pressure and the frequency of respiration also were recorded. A significant blood pressure decrease was concomitant with the respiratory arrest. Under further artificial respiration, the arterial blood pressure increased to normal values.

DISCUSSION

The levels of neuromuscular blocking activity of the three compounds were not directly related to the P···N distance. The correlation between the curare-like potency and the relative dispositions of the onium groups in bis-onium derivatives has been questioned (41–44). It appears that the activity of some pentamethonium iodides (41) or hexa- and decamethonium bromides (42) may arise from the number of van der Waals contacts between the extreme methyl groups and the receptor sites. In addition, it has been postulated that the ether linkages of the tubocurarines are involved in the interaction with the receptor (43, 45–47).

Similarly, for III, V, and VII, the electronic interaction of the phosphonium cation and the formation of hydrogen bonding between the oxygen atom of the morpholine group and the receptor site can be suggested. Thus, the observed P···O distance for the more potent VII is 6.8 Å, in accordance with the known value found for the cholinergic receptors (48–50).

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ACKNOWLEDGMENTS

Supported in part by the Institut National de la Santé et de la Recherche Médicale and in part by the Centre National de la Recherche Scientifique.

The authors thank M. Hurtevent for performing some of the experiments.

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

D. A. VENTURA and H. Y. ANDO ˣ

Received November 29, 1978, from the *Philadelphia College of Pharmacy and Science, Philadelphia, PA 19104.* Accepted for publication March 6, 1980.

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

0022-3549/80/0800-0891$01.00/0