Isotonicity Values and Derived Thermodynamic Properties of Some Uni-Univalent Electrolytes of Pharmaceutical Interest

By RICHARD D. JOHNSON*, FRANK M. GOYAN, and L. D. TUCK

Commonly used substituted amine salts of pharmaceutical interest are studied with the thermoelectric vapor-phase osmometer previously described in *J. Pharm. Sci.* as a molecular weight apparatus. The instrument is used without modification to determine change in the resistance of a thermistor as a function of the concentrations of drops of liquid in contact with it. The data are plotted on a percentage basis to provide direct reading of isotonicity values (per cent NaCl) and on a molar basis to show typical electrolyte behavior at lower concentrations. A few interesting abnormalities, including apparent micelle formation, appear at higher concentrations (0.1–0.2 *M*). Osmotic coefficients and sodium chloridee quivalent values are calculated.

THE INSTRUMENTATION described by two of the present authors (1) as a device for the determination of molecular weight can be used without modification to determine isotonicity values and osmotic coefficients of solutions. The slight deviation from linearity introduced by the thermistor has been shown by Burge (2) to be negligible at the level of accuracy presently sought. Previous papers (3) have presented the general conclusion that the resistance change as observed in this instrument is essentially a measure of a colligative property not significantly different from the elevation of the boiling point. The great advantage of this instrument is that it is convenient to operate at any chosen temperature.

Goyan *et al.* (4) showed that most salts of pharmaceutical interest could be treated as typical electrolytes because of the fact that high accuracy is not required in rendering solutions isotonic. Although dilute solutions of uni-univalent electrolytes may be treated as if they shared the same molal freezing-point lowering (3.4°), Hammarlund and Pedersen-Bjergaard (5) reported several exceptions at higher concentrations based upon their freezing-point measurements. The compounds selected for study in this work include several of these exceptional substances. It seems of interest to discover whether the same behavior occurs at room temperature.

EXPERIMENTAL

The instrumentation and technique of measurement are the same as described earlier (1). All of the compounds used were of good commercial quality. Distilled water was used throughout as the solvent. Solutions were made on a molar basis using an analytical balance and 25-ml. volumetric flasks. Per cent concentrations were calculated on a w/v basis from established molar concentrations and molecular weights. Density determinations were made on 0.1 and 0.2 *M* procaine hydrochloride solutions using a chainomatic specific gravity balance in order to judge the importance of converting to the molal system for further evaluation. It can be shown that the difference between molar and molal concentration is not a matter of critical importance when working at this level of accuracy with dilute aqueous solutions. The temperature of the bath was maintained at 25.00° by the method described in a previous paper (1) and independently read on a mercury-in-glass thermometer graduated in 0.01°

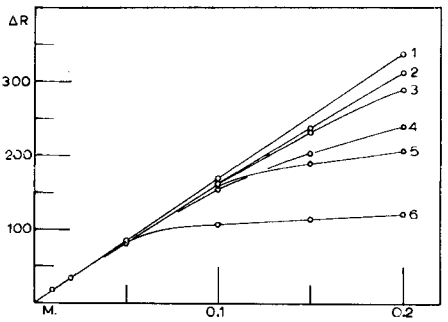

Fig. 1.—ΔR (ohms) *vs.* molar concentration Identities of curves are keyed to Table I. Data are taken from Table II.

TABLE I.—COMPOUNDS STUDIED

Compd. No.	Compd.	Mol. Wt.
1	Sodium chloride	58.45
2	Phenylephrine HCl	203.7
3	Procaine HCl	272.8
4	Diphnehydramine HCl	291.8
5	Tetracaine HCl	300.8
6	Dibucaine HCl	379.9
7	Neostigmine bromide	303.2

Received April 20, 1965, from the School of Pharmacy, University of California, San Francisco.
Accepted for publication May 27, 1965.
Presented to the Scientific Section, A.PH.A., New York City meeting, August 1964.
This investigation was supported by research funds from the University of California and training grant 5-T1-GM-726-01 from the National Institutes of Health, U. S. Public Health Service, Bethesda, Md.
* American Foundation for Pharmaceutical Education Fellow. Recipient of Henry S. Wellcome Memorial Fellowship, 1963–1965.

TABLE II.—OHMS (ΔR) *Versus* MOLAR CONCENTRATIONS (c) FOR COMPOUNDS STUDIED

Compd. No.	c = 0.01	0.02	0.05	0.10	0.15	0.20
1	17.8	34.8	86.0	169.1	...	338.5[a]
2	17.3	34.7	83.3	161.7	238.3	314.0
3	17.1	34.3	83.3	162.0	231.7	280.0
4	17.3	33.9	81.4[a]	152.6[a]	202.7	240.6
5	17.2	34.2	82.0[a]	160.4[a]	190.0	207.0
6	17.4	34.2	82.0	106.8	113.8	121.0
7	16.9	33.9	80.7	152.0	223.3[a]	304.0[a]

[a] Average deviation between 2 and 4 ohms.

TABLE III.—OSMOTIC COEFFICIENTS CALCULATED BY $\phi = \Delta R/K_0c = \Delta R/1830c$

Compd. No.	c = 0.01	0.02	0.05	0.10	0.15	0.20
1	0.970	0.949	0.940	0.924	...	0.925
2	0.945	0.948	0.910	0.884	0.868	0.858
3	0.936	0.936	0.910	0.885	0.844	0.765
4	0.945	0.926	0.890	0.828	0.738	0.657
5	0.940	0.934	0.889	0.876	0.692	0.566
6	0.947	0.936	0.896	0.583	0.415	0.303
7	0.923	0.926	0.882	0.830	0.811	0.841

TABLE IV.—SODIUM CHLORIDE EQUIVALENT VALUES CALCULATED BY EQ. 2

Compd. No.	c = 0.01	0.02	0.05	0.10	0.15	0.20
1	1.05	1.02	1.01	1.00	...	1.00
2	0.29	0.29	0.28	0.27	0.27	0.27
3	0.22	0.22	0.21	0.20	0.20	0.18
4	0.20	0.20	0.19	0.18	0.16	0.14
5	0.20	0.20	0.19	0.18	0.15	0.12
6	0.16	0.16	0.15	0.10	0.07	0.05
7	0.19	0.19	0.18	0.18	0.17	0.17

divisions. A 6-v. battery powered the bridge, causing the drops of pure solvent to be slightly warmer than the bath.

RESULTS

Figure 1 displays all of the compounds studied except neostigmine bromide which crosses curve 3 with a nontypical slope that tends to confuse the figure. Table I lists the numbers used to identify the compounds throughout these tabulations. Table II shows the difference in ohms (ΔR) between the resistance of the thermistor in contact with solvent and the resistance of the same thermistor in contact with the various solutions. All values are the average of three or more separate determinations and show an average deviation not greater than 2 ohms except as indicated. Table III shows osmotic coefficients calculated from these data, and Table IV presents calculated sodium chloride equivalent values.

DISCUSSION

Osmotic coefficients are calculated by dividing the measured ΔR values by a K_0 value and also dividing by molar concentration.

$$\phi = \Delta R/K_0c \qquad \text{(Eq. 1)}$$

K_0 is evaluated by the method used by Burge (2), where ϕ is a known osmotic coefficient for a solution for which ΔR and c are also known. Data from Robinson and Stokes (6) and Burge (2), combined with present measurements on NaCl (Table II) and previous measurements on sucrose (1), yield a weighted average value of $1.83 \pm 0.01 \times 10^3$ for K_0. This value for K_0 is then used to calculate Table III from Table II by the use of Eq. 1. It will be noted that very dilute solutions of all of these substances behave like typical electrolytes, but that above 0.05 M there is evidence to indicate micelle formation. The ones with the more pronounced tendency to have very low osmotic coefficients also have the structure of surfactants, more or less, and seem to lower surface tension. However, a 1% solution of a compound having a molecular weight of 200 is only 0.05 M. Since most substances of this nature have molecular weights above 200, it would seem desirable to replot the data on a percentage concentration basis.

Figure 2 shows the effect of plotting the same data on a w/v percentage basis. It will be noted that all of the high molecular weight compounds give straight lines up to 2%. This, of course, is due to the fact that many of the higher concentrations studied do not appear on the graph. However, the selection of this scale allows for a graphic representation of isotonicity values and sodium chloride equivalents. The isotonicity value (per cent NaCl) (7) for any concentration of any substance can be read off the per cent scale directly under the point on the NaCl line having the same ΔR value. This is illustrated by the directed lines going from 1 and 2% phenylephrine over to the NaCl line and then down to the per cent scale. These intersections are labeled E and 2E, respectively, because "isotonicity value" is defined as the concentration of a solution of NaCl that has the same colligative property as the solution in question (8). Since a 1% solution contains 1 Gm./100 ml., the isotonicity value of a 1% solution is also the sodium chloride equivalent of the sub-

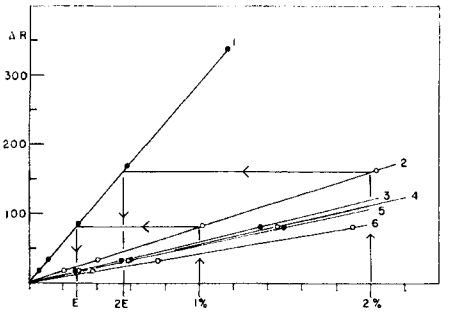

Fig. 2.—ΔR (ohms) *vs.* per cent concentration. The arrows illustrate a graphic method for computing sodium chloride equivalent (E) values.

TABLE V.—COMPARISON SODIUM CHLORIDE EQUIVALENT VALUES (E)

Compd. No.	$58/M$	Table IV (0.05 M)	F.p. (1%)	Table IV[a]	F.p.[b]
2	0.28	0.28	0.32	0.27 *A*	0.30 *A*
3	0.21	0.21	0.21	0.20 *A*	0.18 *A*
4	0.20	0.19	0.28	0.14 *B*	0.17 *B*
5	0.19	0.19	0.18	0.12 *B*	0.12 *B*
6	0.15	0.15	0.13	0.05 *B*	0.08 *B*

[a] In the next to the last column, *A* represents 0.15 *M* and *B* 0.20 *M*. [b] In the last column, *A* represents 3% concentration and *B* 5% concentration.

stance (*i.e.*, that weight of NaCl that has the same colligative potential as does 1 Gm. of the drug) (9).

The graph in Fig. 2 is useful in demonstrating this concept, but analytical methods are more convenient. Since 1% NaCl has a ΔR value of 290, and the curve may be treated as a straight line, $\Delta R/290$ is the isotonicity value corresponding to any value of ΔR. If this is read off for a per cent, P, of the compound, the isotonicity value for a 1% solution is $\Delta R/290P$. Hence, $E = \Delta R/290P$. Per cent (P), however is $cM/10$. Therefore

$$E = \frac{\Delta R \times 10}{290 \times cM} = \frac{\Delta R}{29cM} \qquad \text{(Eq. 2)}$$

where c is the molar concentration, M is the molecular weight of the compound, and E is its NaCl equivalent. This equation was used in calculating Table IV.

When values from Table IV are compared with estimates of E made by Goyan *et al.* (4) on the basis of typical electrolyte behavior ($E = 58/M$), there is almost perfect agreement for 1% solutions. In cases where more concentrated solutions show abnormalities by the freezing point method (5), there is essential agreement between the freezing-point method and this method, although some differences are slightly outside of the limit of error of this method. Table V displays this agreement.

The ΔR values which are proportional to the osmotic coefficient as a function of concentration are shown in Fig. 1 for the various solutes. Deviations of the various curves from that of sodium chloride are assumed to be due to micelle or molecular aggregate formation. The osmotic data may be used by the methods discussed by Phillips (10) and Philippoff (11) to estimate the number of monomer units making up the micelles. This will be the subject of a future paper.

CONCLUSIONS

The thermoelectric vapor phase osmometer originally described as a molecular weight apparatus is an excellent instrument for measuring osmotic coefficients, isotonicity values, and sodium chloride equivalents. All of the substituted amines studied show normal behavior in very dilute solutions. The present measurements are in better agreement with theoretical estimates than are freezing point data for 1% solutions. However, significant deviations from usual electrolyte behavior occur at higher concentrations indicating solute association or micelle formation. Both methods are in approximate agreement in this region.

REFERENCES

(1) Goyan, F. M., and Johnson, R. D., *J. Pharm. Sci.*, **53**, 328(1964).
(2) Burge, D. E., *J. Phys. Chem.*, **67**, 2590(1963).
(3) Goyan, F. M., and Johnson, R. D., *J. Pharm. Sci.*, **52**, 390(1963).
(4) Goyan, F. M., Tuck, L. D., and Taylor, P. L., *ibid.*, **50**, 684(1961).
(5) Hammarlund, E. R., and Pedersen-Bjergaard, K., *J. Am. Pharm. Assoc., Sci. Ed.*, **47**, 107(1958).
(6) Robinson, R. A., and Stokes, R. H., "Electrolyte Solutions," 2nd ed., Butterworths Publications Ltd., London, England, 1959, pp. 30, 483.
(7) Goyan, F. M., *Proc. A. A. C. P. Teacher's Seminar*, **13**, 92(1961).
(8) Goyan, F. M., and Reck, D., *J. Am. Pharm. Assoc., Sci. Ed.*, **44**, 44(1955).
(9) Szekely, I., and Goyan, F. M., *ibid.*, **41**, 31(1952).
(10) Phillips, J. N., *Trans. Faraday Soc.*, **51**, 561(1955).
(11) Philippoff, W., *Discussions Faraday Soc.* (No. 11), **1951**, 96.