# Apparent Molal Volumes of Lidocaine−HCl and Procaine−HCl in Aqueous Solution as a Function of Temperature

**Daniel R. Torres, Luis H. Blanco,[†] Fleming Martínez,[‡] and Edgar F. Vargas*[,§]**

Laboratorio de Investigaciones Básicas, Departamento de Química, Universidad Nacional de Colombia, A.A. 14490, Bogotá D.C., Colombia, Grupo de Investigaciones Farmacéutico-Fisicoquímicas, Departamento de Farmacia, Universidad Nacional de Colombia, A.A. 14490, Bogotá D.C., Colombia, and Laboratorio de Termodinámica de Soluciones, Departamento de Química, Universidad de los Andes, Bogotá D.C., Colombia

Apparent molal volumes of two local anesthetics, lidocaine HCl and procaine HCl, in water at (298.15, 303.15, and 310.15) K have been measured in the concentration range from (0.01 to 0.1) mol·kg$^{-1}$. The densities were obtained with a magnetic float densimeter. The concentration dependence of $V_\phi$ has been calculated using the Redlich and Meyer equation. The values of apparent molal volumes at infinite dilution, $V_\phi^0$, the empirical constants $B_V$, and the partial molal expansibilities, $E_\phi^0$, were calculated. The results are interpreted in terms of competitive effects between electrostriction and hydrophobic solvation.

## Introduction

Local anesthetics are amphiphilic molecules that have hydrophobic and hydrophilic domains that are separated by an intermediate alkyl chain. The hydrophilic group can be a tertiary or secondary amine, and the hydrophobic domain is an aromatic residue. They are classified as an ester type or amide type; it depends on the group that binds to the aromatic residue. The nature of this bond determines several pharmacological properties of these drugs.[1]

The characterization of local anesthetics in aqueous solutions has been the object of study due to their widespread application in treating pain. It is widely accepted that local anesthetics exert their pharmacological action by interacting with lipid molecules constituting a biological membrane. The mechanism of these interactions, however, is not clearly understood. The role of local anesthetics has been attributed to an increase in the surface pressure of the lipid layer that constitutes the nerve membrane, closing the pores through which the channels, responsible for the increase in cellular permeability to $Na^+$, $K^+$, or $Ca^{2+}$ ions, pass.[1−8] It has been suggested that local anesthetics affect permeability by increasing the degree of disorder of the membrane.[9] Thus, the volumetric properties of anesthetics have an important role in the mechanism of anesthesia, and the determination of volumetric properties of local anesthetics in aqueous solutions provides information needed to understand the mechanism of anesthesia. In the literature, a few studies on the volumetric properties of local anesthetics have been reported.[10−12]

In the present work, we study two local anesthetics, lidocaine HCl and procaine HCl, in aqueous solutions, and the molecular structures are shown in Figure 1. The apparent molal volumes as a function of concentration were measured at (298.15, 303.15, and 310.15) K. The range of concentrations was (0.01 to 0.10) mol·kg$^{-1}$. The densities were measured using the magnetic float technique. The data are discussed in terms of relative solvation of these compounds.

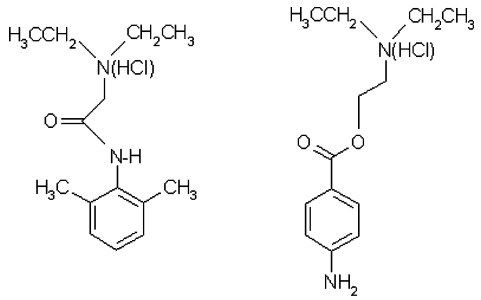


**Figure 1.** Molecular structures of lidocaine-HCl (LD-HCl) and procaine-HCl (PC-HCl).

## Experimental Section

***Materials.*** The local anesthetics, procaine (PC-HCl) and lidocaine (LD-HCl), were USP quality,[13] and they were used without further purification. The KCl used was obtained from Merck and used after drying for 24 h at 373 K. All solutions were prepared by weight at room temperature using an Ohaus Analytical Plus balance with precision of 0.01 mg. Water was doubly distilled, treated according to a method cited in the literature,[14] and degassed before use to prevent the formation of bubbles on the magnetic float during a run.

***Densities.*** The densities of the aqueous anesthetic solutions were measured with an uncertainty of ± 0.000001 g·cm$^{-3}$, using a magnetic float densimeter. It was constructed on the basis of another magnetic float densimeter, which has been described elsewhere.[15]

The operational procedure and calibration of the densimeter were made according to the literature.[15−17] The repeatability of the densimeter was checked several times using water. The density of water, $\rho_0$, at different temperatures was taken from Patterson and Morris.[18] The standard deviation of the value of the equilibrium current under different conditions was found to be ± 0.02 mA which corresponds in density units to ±

* Corresponding author. E-mail: edvargas@uniandes.edu.co.
[†] Departamento de Química, Universidad Nacional de Colombia.
[‡] Departamento de Farmacia, Universidad Nacional de Colombia.
[§] Departamento de Química, Universidad de los Andes.

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**Table 1. Densities of Aqueous Solution of KCl**

| concentration | $\rho_{KCl}$ exptl | $\rho_{KCl}$ |
|---|---|---|
| mol·kg$^{-1}$ | g·cm$^{-3}$ | g·cm$^{-3}$ |
| | 298.15 K | |
| 0.030601 | 0.998491 ± 0.000001 | 0.998496[a] |
| | | 0.998491[b] |
| | 303.15 K | |
| 0.01050 | 0.996131 ± 0.000001 | 0.996151[c] |
| 0.02061 | 0.996605 ± 0.000001 | 0.996629[c] |

[a] Ref 15. [b] Ref 19. [c] Ref 20.

0.000001 g·cm$^{-3}$. This value was the same at all the temperatures studied.

The accuracy of the densimeter was checked by measuring the densities of aqueous solutions of KCl. The results are shown in Table 1. The values interpolated from Smith,[19] Laliberté and Cooper,[20] and Blanco and Vargas[15] are also listed, and good agreement with the literature was found.

## Results and Discussion

The densities of aqueous solutions of PC-HCl and LD-HCl were measured at (298.15, 303.15, and 310.15) K using a magnetic float densimeter. The apparent molal volumes, $V_\phi$, of these solutions were calculated from the equation

$$V_\phi = \frac{M}{\rho} - \frac{1000(\rho - \rho_0)}{m\rho\rho_0} \quad (1)$$

where $M$, $m$, $\rho$, and $\rho_0$ are the molar mass of solute, molal concentration (mol·kg$^{-1}$), and densities of the solution and the solvent, respectively. Tables 2 and 3 summarize the results of the difference between the density of water and the density of the solutions at several molal concentrations, the apparent molal volumes of the solutes, their concentrations, and their uncertainties, $\sigma_V$, at all temperatures considered. To determine the uncertainty in $V_\phi$, the law of propagation of uncertainties was used.[21]

The molal concentration dependence of $V_\phi$, at each temperature, was fitted to an equation of the type[22]

$$V_\phi = V_\phi^0 + S_V m^{1/2} + B_V m \quad (2)$$

where $V_\phi^0$ is the apparent molal volume at infinite dilution (equal to the limiting partial molal volume $V_2^0$); $S_V$ is the Debye−Hückel limiting slope (values of (1.8743, 1.9616, and 2.0934) cm$^3$·mol$^{-3/2}$·kg$^{1/2}$ for a 1:1 electrolyte at (298.15, 303.15, and 310.15) K, respectively, were used);[23] and $B_V$ is an empirical constant. The values of $V_\phi^0$ and $B_V$ were obtained at each temperature using weighted least-squares. The numerical values of $V_\phi^0$ and $B_V$, to LD-HCl and PC-HCl, together with their uncertainties and the uncertainty in the regression, $\sigma$, are listed in Table 4. The values of $V_\phi^0$ reported by other authors are also shown.

The apparent molal volume at infinite dilution, $V_\phi^0$, of organic ions in aqueous solutions can be divided into four main contributions[24,25]

$$V_\phi^0 = \bar{V}(\mathrm{IN}) + \bar{V}V(\mathrm{COUL}) + \bar{V}(\mathrm{STR}) + \bar{V}(\mathrm{HB}) \quad (3)$$

where $\bar{V}$(IN) is the intrinsic property; $\bar{V}$(COUL) is the electrostriction of the solvent caused by the Coulombic interactions between water and the ion (negative effect); $\bar{V}$(STR) is the structural contribution to the volume due to changes in the structure of water as a cavity formation (negative effect) and any increase in "icelikeness" of water (positive effect); and $\bar{V}$(HB) is the contribution arising from hydrogen bonding of the solute to water. The contribution of $\bar{V}$(COUL) and $\bar{V}$(STR) to $V_\phi^0$ can be considered by the contribution of the following effects: (1) The influence of the electrical field on the water molecules around the ion. Its field tends to orient the water molecules through ion−dipole interactions and further ion−multipole interactions until the latter becomes negligible at the distances involved.[26] (2) The orientation of water molecules, to set the favorable geometry, has to have the three-dimensional hydrogen-bonded network, according to the tetrahedral structure of bulk water. Thus, if the ion contains nonpolar groups, this effect, as indicated by Marcus,[26] will extend as near to the ion as the competition with the other effect will permit. In consequence, if the ion has nonpolar groups, they may shield the region near the ion from disruption of its structure and hence enhance the tetrahedral structure in this region.[26] Therefore, the structuring of water will depend on the ion, its size and shape, and the number of nonpolar groups. As a consequence, the partial molal volumes are known to be sensitive to solute solvation, and it provides information about the structural volume of the solute in the solvent and the volume change of the solvent in the process of shell formation around the ion.[27] Several authors[25,27−29] have related $V_\phi^0$ with a quantitative expression of the interactions of the solute with its environment, that is, solute−solvent interactions. On the other hand, the dependence of the partial molal volumes can be used to study ion−ion interactions. In this way, $B_V$ has been related to solute−solute interactions due to nonelectrostatic forces.[25,27]

The sign of the parameter $B_V$ has been associated in several ways, such as, for example, to the presence of dimers in the

**Table 2. Apparent Molal Volumes of Aqueous Solutions of Lidocaine-HCl**

| molality | $-1000\Delta\rho$ | $V_\phi$ | $\sigma_v$ |
|---|---|---|---|
| mol·kg$^{-1}$ | g·cm$^{-3}$ | cm$^3$·mol$^{-1}$ | cm$^3$·mol$^{-1}$ |
| | 298.15 K | | |
| 0.01229 | 0.4101 | 237.98 | 0.08 |
| 0.02576 | 0.8701 | 237.45 | 0.03 |
| 0.03530 | 1.1911 | 237.382 | 0.029 |
| 0.04637 | 1.5801 | 236.960 | 0.022 |
| 0.05530 | 1.8821 | 236.938 | 0.018 |
| 0.05999 | 2.0431 | 236.864 | 0.017 |
| 0.06587 | 2.2481 | 236.747 | 0.015 |
| 0.07533 | 2.5591 | 236.830 | 0.014 |
| 0.08682 | 2.9431 | 236.817 | 0.012 |
| 0.09518 | 3.2191 | 236.831 | 0.011 |
| 0.09984 | 3.3711 | 236.847 | 0.010 |
| | 303.15 K | | |
| 0.01045 | 0.3368 | 239.14 | 0.10 |
| 0.02049 | 0.6648 | 238.98 | 0.05 |
| 0.03038 | 0.9938 | 238.68 | 0.03 |
| 0.04052 | 1.3188 | 238.786 | 0.025 |
| 0.05004 | 1.6488 | 238.318 | 0.020 |
| 0.06004 | 1.9688 | 238.406 | 0.017 |
| 0.06931 | 2.2888 | 238.108 | 0.015 |
| 0.07916 | 2.6058 | 238.139 | 0.013 |
| 0.08916 | 2.9388 | 238.021 | 0.012 |
| 0.09984 | 3.2958 | 237.886 | 0.010 |
| | 310.15 K | | |
| 0.01026 | 0.3183 | 241.07 | 0.10 |
| 0.02040 | 0.6533 | 239.99 | 0.05 |
| 0.03014 | 0.9943 | 238.94 | 0.03 |
| 0.04052 | 1.3333 | 238.967 | 0.025 |
| 0.05228 | 1.6893 | 239.477 | 0.020 |
| 0.06294 | 2.0613 | 238.936 | 0.016 |
| 0.06918 | 2.2593 | 238.983 | 0.015 |
| 0.08014 | 2.6073 | 239.032 | 0.013 |
| 0.09504 | 3.0873 | 238.962 | 0.011 |
| 0.10110 | 3.2763 | 239.002 | 0.010 |

**Table 3. Apparent Molal Volumes of Aqueous Solutions of Procaine-HCl**

| molality | $-1000\Delta\rho$ | $V_\phi$ | $\sigma_v$ |
|---|---|---|---|
| mol·kg$^{-1}$ | g·cm$^{-3}$ | cm$^3$·mol$^{-1}$ | cm$^3$·mol$^{-1}$ |
| | 298.15 K | | |
| 0.01006 | 0.5101 | 222.50 | 0.10 |
| 0.01028 | 0.5221 | 222.41 | 0.10 |
| 0.02020 | 0.9881 | 224.19 | 0.05 |
| 0.02924 | 1.4121 | 224.69 | 0.04 |
| 0.03864 | 1.8581 | 224.803 | 0.026 |
| 0.04500 | 2.1581 | 224.867 | 0.023 |
| 0.05697 | 2.7271 | 224.825 | 0.018 |
| 0.06965 | 3.3251 | 224.816 | 0.015 |
| 0.08017 | 3.8051 | 224.986 | 0.013 |
| 0.09220 | 4.3711 | 224.915 | 0.011 |
| | 303.15 K | | |
| 0.01028 | 0.4868 | 225.89 | 0.10 |
| 0.02051 | 0.9598 | 226.41 | 0.05 |
| 0.03015 | 1.4158 | 226.23 | 0.03 |
| 0.03837 | 1.8028 | 226.119 | 0.026 |
| 0.04622 | 2.1548 | 226.399 | 0.022 |
| 0.05666 | 2.6128 | 226.817 | 0.018 |
| 0.06784 | 3.1348 | 226.611 | 0.015 |
| 0.08065 | 3.7088 | 226.714 | 0.013 |
| 0.08987 | 4.1058 | 226.924 | 0.011 |
| 0.09982 | 4.5768 | 226.653 | 0.010 |
| | 310.15 K | | |
| 0.01015 | 0.5003 | 224.57 | 0.10 |
| 0.02012 | 0.9783 | 225.11 | 0.05 |
| 0.02798 | 1.3283 | 226.17 | 0.04 |
| 0.03581 | 1.6703 | 226.955 | 0.028 |
| 0.04996 | 2.3153 | 227.117 | 0.020 |
| 0.06012 | 2.7733 | 227.235 | 0.017 |
| 0.07014 | 3.2243 | 227.281 | 0.015 |
| 0.08065 | 3.6963 | 227.323 | 0.013 |
| 0.09026 | 4.1223 | 227.380 | 0.011 |
| 0.10034 | 4.5793 | 227.311 | 0.010 |

**Table 4. Apparent Molal Volumes at Infinite Dilution and $B_V$ Parameters of Aqueous Solutions of Lidocaine-HCl and Procaine-HCl**

| temp | $V_\phi^0$ | $B_V$ | $\sigma$ |
|---|---|---|---|
| K | cm$^3$·mol$^{-1}$ | cm$^3$·kg·mol$^{-2}$ | cm$^3$·mol$^{-1}$ |
| | Lidocaine-HCl | | |
| 298.15 | 237.83 ± 0.13 | −20.3 ± 2.7 | 0.243 |
| | 240.5[b] | | |
| 303.15 | 239.10 ± 0.06 | −19.9 ± 1.4 | 0.114 |
| 308.15 | 240.2 ± 1.2[c] | − | − |
| 310.15 | 240.6 ± 0.4 | −31.2 ± 8.0 | 0.677 |
| | Procaine-HCl | | |
| 298.15 | 224.45 ± 0.09 | −0.9 ± 1.3 | 0.062 |
| | 225.84 ± 0.03[a] | | |
| | 225.5[b] | | |
| 303.15 | 225.98 ± 0.21 | 2.0 ± 2.6 | 0.172 |
| 308.15 | 226.63 ± 0.15[c] | − | − |
| 310.15 | 226.68 ± 0.10 | 0.2 ± 1.2 | 0.059 |

[a] Ref 10. [b] Ref 11. [c] Ref 12.

premicellar region,[27] to hydrophobic interactions due to disturbance of the bulk water structure by the hydrophobic skeleton of the solute,[25] and to electrostriction effects due to overlapping of ionic hydration spheres.[28−30] Positive values of $B_V$ were found for the amphiphilic drugs such as penicillin V,[31] nortriptyline,[32] promazine, and chlorpromazine[33] and some tetraalkylammonium bromides, especially tetramethyl and tetraethyl.[30] Negative values of $B_V$ were found in aqueous solutions of propranolol and acebutolol,[27] thioridazine hydrochloride,[25] phenalalkylamines,[34] *n*-alkylamine hydrobromides,[24] and tetraalkylammonium bromides.[30,35]

Procaine-HCl and lidocaine-HCl show a complex structure with several polar sites dispersed among hydrophobic regions.

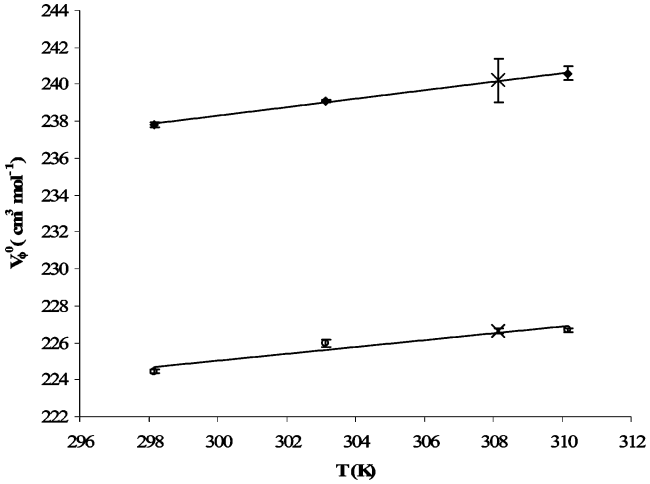


**Figure 2.** Apparent molal volumes at infinite dilution as a function of temperature for aqueous solutions of: ◆, LD-HCl; ○, PC-HCl; ×, ref 12.

The presence of $N^+$ centers suggests a significant electrostriction term in their volumes; however, just as found by Laliberté and Conway,[36] the relative electrostriction effect caused by the positive charge on the nitrogen center is attenuated when alkyl groups are present. They found that when R is larger than $C_2H_5$, the electrostriction effect in the $R_2NH_2Cl$ series is virtually eliminated; a similar behavior was observed with trialkylammonium ions. Thus, the electrostriction effect caused by the presence of positive nitrogen centers in PC-HCl and LD-HCl is shielded by the $C_2H_5$ groups. On the other hand, the hydrophobicity of the dimethylphenyl group in LD-HCl virtually eliminates the electrostriction caused by the RNHCOR segment. Similar behavior is expected to occur on the RCOOR segment by the presence of the aromatic ring in the PC-HCL molecule. Nevertheless, it is expected that the presence of the $-NH_2$ group over the phenyl ring of PC-HCl contributes to $\bar{V}$(HB), and in consequence, the electrostriction effect has a negative effect on $V_\phi^0$.

The variations of $V_\phi^0$ with temperature for both local anesthetics are given in Figure 2. A linear dependence was found for both. The apparent molal expansibilities at infinite dilution, $E_\phi^0 = \partial V_\phi^0/\partial T$, were (0.191 ± 0.024) cm$^3$·mol$^{-1}$·K$^{-1}$ and (0.246 ± 0.010) cm$^3$·mol$^{-1}$·K$^{-1}$ for PC-HCl and LD-HCl, respectively. Figure 2 shows good agreement between the data presented in this study and the data reported by Iqbal et al.,[12] who only reported data at 308.15 K.

The $E_\phi^0$ can be represented by two major components[29,37]

$$E_\phi^0 = E^0(\mathrm{COUL}) + E^0(\mathrm{STR}) \qquad (4)$$

At low temperatures, the structural partial molal component is the predominant factor, and at high temperatures, the electrostatic partial molal component is the predominant factor. The results obtained in this work show that $E_\phi^0$ is independent of temperature. According to Millero,[29] we can conclude that the temperature does not have a significant effect on the outer hydrated water molecules.

The LD-HCl shows negative $B_V$ values for all temperatures (see Table 4), whereas the PC-HCl has a negligible value of $B_V$ at all temperatures considered (see Table 4). The negative value of $B_V$ for LD-HCl can be attributed to the major contribution of hydrophobic hydration over the electrostriction effects caused by the presence of polar groups, thus the long-range hydrophobic interactions are favored. This result is according with Matsuki et al.[11] and Iqbal et al.[12] who studied several local anesthetics

at (25 and 35) °C, respectively. The behavior of PC-HCl can be explained by the competitive effects between the enhancement of the water structure and the electrostriction effect due to the presence of the hydrophilic group $-NH_2$.

The anesthetic potency of LD-HCl and PC-HCl has been related to the hydrophobicity of the molecules.[1] It is suggested that the site of action of local anesthetics is at the cell membrane and that the interaction between nonpolar groups is of primary importance.[38] In this way, Fraceto et al.[39] have related the pharmacodynamics with the capacity of anesthetics to insert into the lipid layer, and this insertion produces an organizational disturbance which interferes with ionic interchange. Matsuki et al.[11] mentioned that the hydrophobicity of the anesthetics is proportional to the facility of partitioning the anesthetics into the membranes. Thus, the anesthetic action of LD-HCl is greater than that of PC-HCl due to its more extensive hydrophobic character. This result is in good agreement with the literature.[11,40]

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