Ionic Partition Diagram of the Zwitterionic Antihistamine Cetirizine

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A recent analysis of the lipophilicity profile of cetirizine in the octanol/water and dodecane/water systems revealed a partial intramolecular charge neutralization that can partly explain why cetirizine has pharmacokinetic properties differing from those of first-generation antihistamines such as hydroxyzine. As conformational changes are the principal driving force for this intramolecular effect, the present study deals with the partitioning of cetirizine and hydroxyzine in an apolar medium well-suited to reveal intramolecular interactions, namely the 1,2-dichloroethane/water system. The lipophilicity of the different electrical forms of cetirizine and hydroxyzine was studied by two-phase titrimetry and cyclic voltammetry. The differences in lipophilicity between the dicationic, monocationic, zwitterionic, and anionic species of cetirizine indicated intramolecular interactions *via* folded conformations, which render the molecule markedly more lipophilic than expected at physiological pH. Folded conformations were also found to predominate in monocationic and neutral hydroxyzine. The ionic partition diagram of cetirizine indicates that it acts as a proton transporter across interfaces under certain conditions of pH and *Galvani* potential difference. This study underlines the importance of conformational effects on the partition properties of cetirizine and hydroxyzine, as well as the complexity of its interfacial mechanisms of transfer. In particular, cetirizine can facilitate proton transfer, a property of potential biological relevance.

1. Introduction[1]). – Antagonism at histaminergic H_1-receptors is one of the major therapeutic strategies in the treatment of allergy. Owing to their high lipophilicity, sedation has been a major disadvantage to the use of the first-generation H_1-antagonists such as hydroxyzine [1–3]. Therefore, a novel class of H_1-receptor antagonists has been developed that show an improved balance between central

[1]) *Abbreviations:* pK_a: dissociation constant in the aqueous phase; $\Delta_o^w\phi$: *Galvani* potential difference between the phases w and o; $\Delta_o^w\phi_i^0$: standard potential of transfer of ion *i* between the phases w (water) and o (octanol); $\Delta_o^w\phi_i^{1/2}$: half-wave potential of ion *i* between the phases w and o; $\Delta G_{tr,i}^{0,w\rightarrow o}$: standard *Gibbs* energy of transfer of ion *i* from phase w to phase o; ITIES: interface between two immiscible electrolyte solutions; $\log P_{oct}^{B}$ (resp. $\log P_{oct}^{XH}$): partition coefficient of neutral hydroxyzine (resp. zwitterionic cetirizine) in the octanol/H_2O system; $\log P_{dce}^{B}$ (resp. $\log P_{dce}^{XH}$): partition coefficient of neutral hydroxyzine (resp. zwitterionic cetirizine) in the 1,2-dichloroethane/H_2O system; $\log D_{dce}$: distribution coefficient in the 1,2-dichloroethane/H_2O system; $\log P_{dce}^{0,i}$: standard partition coefficient of ion *i* in the 1,2-dichloroethane/H_2O system; QMD: quenched molecular dynamics; *R*: gas constant; *F*: *Faraday* constant; *T*: temperature; K_Z: tautomeric equilibrium constant of zwitterion; XH: zwitterionic cetirizine; XH_2^+: monoprotonated cetirizine; XH_3^{2+}: diprotonated cetirizine; X^-: anionic cetirizine; B: neutral hydroxyzine; BH^+: monoprotonated hydroxyzine; BH_2^{2+}: diprotonated hydroxyzine; $\Delta\log P_{oct\text{-}dce}^{B}$: $\log P_{oct}^{B} - \log P_{dce}^{B}$; $\Delta\log P_{oct\text{-}dce}^{XH}$: $\log P_{oct}^{XH} - \log P_{dce}^{XH}$; *diff* ($\log P_{dce}^{B\text{-}i}$): $\log P_{dce}^{B} - \log P_{dce}^{0,i}$; *diff* ($\log P_{dce}^{XH\text{-}i}$): $\log P_{dce}^{XH} - \log P_{dce}^{0,i}$; z_i: charge of ion *i*.

nervous system (CNS) and peripheral effects. Cetirizine was introduced in 1987 and belongs to these second-generation antihistamines [4][5].

Recently, the ionization and lipophilicity behavior of cetirizine and hydroxyzine (*Fig. 1*) were examined in two isotropic media, namely the octanol/H_2O and the dodecane/H_2O [6]. It was shown that cetirizine exists as a zwitterion in the broad pH region of 3.5–7.5 and presents a relatively low lipophilicity (log $P_{oct}^{XH} = 1.5$) compared to cationic antihistamines like hydroxyzine. A careful analysis of the lipophilicity profile of cetirizine in these media revealed a partial intramolecular charge neutralization, which might explain why cetirizine is lipophilic enough to be well-absorbed orally but hydrophilic enough to have a minute cerebral uptake, resulting in a low incidence of CNS effects such as sedation and somnolence.

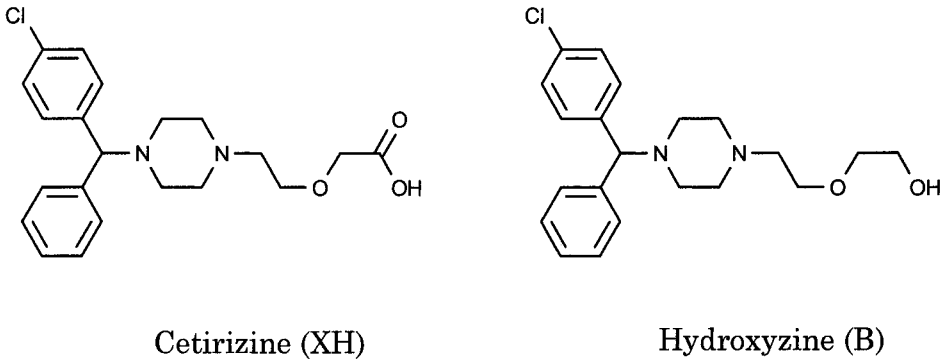


Fig. 1. *Molecular structures of cetirizine and hydroxyzine*

As conformational changes are the principal driving forces for this intramolecular effect [7], the present study examines the partitioning of cetirizine and hydroxyzine in an apolar medium well-suited to reveal intramolecular interactions, namely the 1,2-dichloroethane/H_2O system [8]. Cyclic voltammetry coupled with potentiometry was used to determine the complete lipophilicity profiles. The results are consistent with QMD study [9] and confirm that strong conformational effects act on the partitioning of the different electrical species of cetirizine and hydroxyzine and may influence their pharmacokinetic behavior. The ionic partition diagram of cetirizine underlines that the mechanisms of transfer of this antihistaminic drug through the interface are potential- and pH-dependent and may be complex, including proton-assisted transfer.

2. Theory. – As most drugs are ionizable compounds, the partitioning behavior of ions cannot be neglected and indeed plays an important role in their pharmacokinetics [10]. Relatively few methods are available to measure the partition of ions. Potentiometry and the shake-flask method are both strongly dependent on experimental conditions, and only an apparent partition coefficient is measured, which depends, for example, on the electrolytes present and on the volume ratio between the aqueous and the organic phase [11][12].

Cyclic voltammetry at the ITIES is a potential-controlled electrochemical experiment, where the current associated with ion-transfer reactions is measured. Two

immiscible liquids (here, 1,2-dichloroethane and H_2O) are put into contact, and a cyclic potential sweep is imposed by the use of two reference electrodes. The polarization of the ITIES induces the movement of ions. The resulting current is measured with two counter-electrodes. Analysis of the current response can give information about the thermodynamics, kinetics, and mechanisms of the ion-transfer reactions across the liquid-liquid interface. In particular, the standard transfer potential of an ion i ($\Delta_o^w\phi_i^0$) can be measured and allows calculation of its standard *Gibbs* energy of transfer ($\Delta G_{tr,i}^{0,w\to o}$), and its standard partition coefficient ($\log P_{dce}^{0,i}$) according to the following equations:

$$\Delta_o^w\phi_i^0 = \frac{\Delta G_{tr,i}^{0,w\to o}}{z_i F} \tag{1}$$

$$\log P_{dce}^{0,i} = -\frac{\Delta G_{tr,i}^{0,w\to o}}{2.3\,RT} \tag{2}$$

where $\log P_{dce}^{0,i}$ represents the partition coefficient of ion i when the interface is not polarized. It depends neither on the difference in potential at the ITIES (*i.e.,* the *Galvani* potential difference noted $\Delta_o^w\phi$), nor on supporting electrolytes or phase ratio. When concentrations, activity coefficients, and standard *Gibbs* transfer energies of all the ions in the system, the volume of each phase, and the temperature are known, $\Delta_O^W\phi$ can be determined [13]. The apparent partition coefficient of i ($\log P_{dce}^{i}$), which corresponds to the partition coefficient obtained by an independent method such as the shake-flask protocol, can then be obtained from *Eqn. 3*.

$$\log P_{dce}^{i} = \log P_{dce}^{0,i} + \frac{z_i F \Delta_o^w\phi}{2.3\,RT} \tag{3}$$

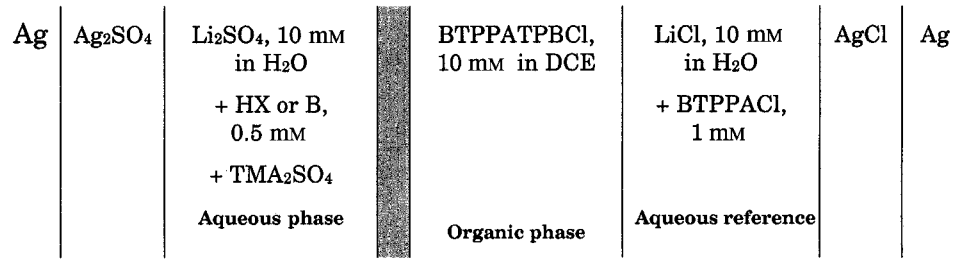
3. Material and Methods. – 3.1 *Compounds.* Two compounds (*Fig. 1*) were examined in this study, namely cetirizine (XH) and hydroxyzine (B). Both were supplied by *UCB* (Braine-l'Alleud, Belgium). 1,2-Dichloroethane (*Romi* Ltd. Cambridge, UK) was used without further purification and handled with all necessary precautions [14]. Bis(triphenylphosphoranylidene)ammonium tetrakis(4-chlorophenyl)borate (BTPPATPBCl) was prepared by metathesis of potassium tetrakis(4-chlorophenyl)borate (*Fluka AG*, Buchs, Switzerland) and of bis(triphenylphosphoranylidene)ammonium chloride (*Aldrich,* Milwaukee, USA) [15]. All other chemicals were of anal. grade and supplied by *Fluka*.

3.2 *Potentiometry Measurements.* The partition coefficients in the 1,2-dichloroethane/H_2O system of the neutral forms of cetirizine and hydroxyzine were measured by potentiometry, with the *PCA 101* instrument of *Sirius Analytical Instruments* (Forrest Row, UK). Solns. of cetirizine or hydroxyzine (0.5 to 1.5 mM, plus 0.15M KCl), initially acidified with HCl to pH 1.8, were titrated from pH 1.8 to 11 in presence of different volumes of 1,2-dichlorethane (*v/v* for 1,2-dichloroethane/H_2O ranging from 0.12 to 1). Titrations were conducted under Ar at $25 \pm 0.1°$.

The $\log P$ values were estimated from difference *Bjerrum* plots [16] and refined by a non-linear least-squares procedure by including previous determined pK_a values as unrefined contributions [6]. The detailed experimental procedures can be found in [17][18].

3.3 *Cyclic-Voltammetry Measurements.* The partition coefficients of the charged forms of cetirizine and hydroxyzine as well as their mechanisms of transfer at the 1,2-dichloroethane/H_2O interface, were studied by cyclic voltammetry with the electrochemical cell shown below.

The experimental setup used was a homemade four-electrode potentiostat, as described in [19], with ohmic-drop compensation [20]. The scanning of the applied potential was performed by a waveform generator (VA scanner *E612, Metrohm*, Herisau, Switzerland), coupled to an *X-Y* recorder (*Bausch & Lomb,* Rochester, NY, USA). Both the cell and the four-electrode potentiostat were housed in a *Faraday* cage. All experiments were carried out at r.t. (25°).



Cetirizine (respectively, hydroxyzine; 0.5 mM) was dissolved in the aq. phase, and its transfer was examined between pH 0.5 and 11.5. In this paper, an increase of the *Galvani* potential difference applied between the aq. and the org. phases (noted $\Delta_o^w\phi$) renders the aq. phase more positive than the org. phase. This increase of $\Delta_0^w\phi$ creates a flow of positive charge from H_2O to the 1,2-dichloroethane phase, which is taken as a positive current.

All half-wave potentials measured (noted $\Delta_o^w\phi_i^{1/2}$) were referred to the half-wave potential of Me_4N^+ ($\Delta_o^w\phi_{Me_4N^+}^{1/2}$). Thus, the standard potential of transfer of an ion i ($\Delta_o^w\phi_i^0$) can be calculated with *Eqn. 4* [21].

$$\Delta_o^w\phi_i^{1/2} - \Delta_o^w\phi_{Me_4N^+}^{1/2} = \Delta_o^w\phi_i^0 - \Delta_o^w\phi_{Me_4N^+}^0 \quad (4)$$

Since the value of $\Delta_o^w\phi_{Me_4N^+}^0$ is known (160 mV on the tetraphenylarsonium tetraphenylborate scale [22]), the standard *Gibbs* energy of transfer of ion i ($\Delta G_{tr,i}^{0,w\to o}$) and its standard partition coefficient ($\log P_{dce}^{0,i}$) can be calculated with Eqns. 1 and 2.

4. Results. – 4.1. *Study of the Voltammograms. Cetirizine.* Representative voltammograms for the transfer of cetirizine at the 1,2-dichlorethane/H_2O interface are shown in *Fig. 2*.

1) At low pH (below 1.35), only one peak appears and is due to the transfer of XH_3^{2+}. The shape of the voltammograms indicates that the transfer is reversible and diffusion-controlled. The peak-to-peak potential difference extrapolated to zero sweep rate is equal to 30 mV and does not depend on the pH, confirming thus the transfer of a dicharged species. The standard transfer potential is estimated as the mid-peak potential and was measured to be 10 mV.

2) When pH increases, the peak of XH_3^{2+} disappears, and two new peaks are detected. The half-wave potential of the wave of lower potential shifts toward lower potential values. This wave is due to the transfer of XH_3^{2+} (w), which loses one proton upon transfer to the organic phase. The half-wave potential of the second wave displays the opposite behavior and can be attributed to the transfer of a proton to the organic phase, assisted by XH_2^{2+} (o), which acts as a proton acceptor. Unfortunately, these two waves are not sufficiently separated to allow the determination of the *Gibbs* potential energies of transfer.

3) Between pH 2.19 and 2.93, the peak of XH_3^{2+} is no longer observable. A new wave appears, with a peak-to-peak separation of around 60 mV. It is due to the transfer of XH_2^+.

4) At pH between 2.93 and 8.0, the peaks of XH_2^+ and of the transfer of the proton assisted by XH_2^+ (o) progressively disappear. At pH 4, no wave can be observed, the neutral zwitterionic form being the major species.

5) Above pH 8.00, a new wave appears at very low potentials. The half-wave potential does not appear to depend on pH, and the peak-to-peak separation is nearly 60 mV. This wave can be attributed to the transfer of X^-. Unfortunately, the

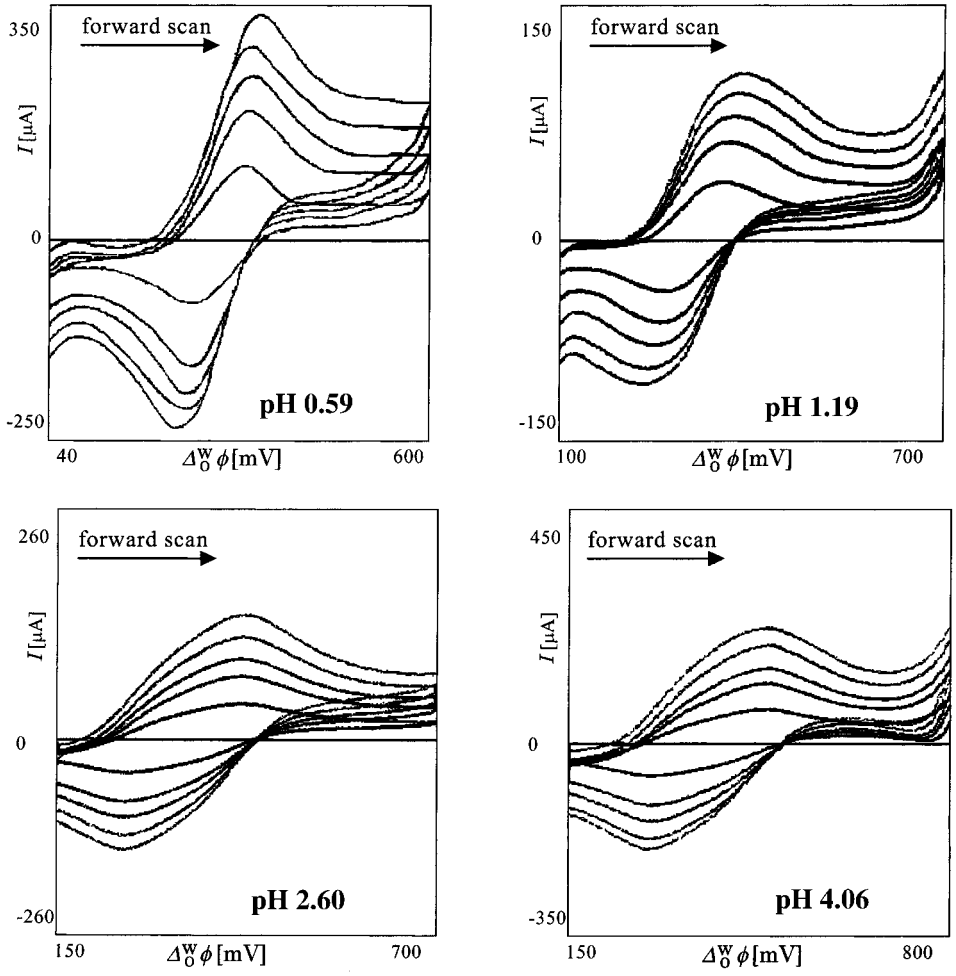


Fig. 2. *Representative cyclic voltammograms of cetirizine.* At each pH, the potential scan rates are 30, 50, 80, and 100 mV/s.

transferring species does not easily cross the interface but remains trapped at the 1,2-dichlorethane/H_2O interface. Thus, the shape of the wave does not allow precise measurement of the half-wave potential. It gives only an estimate of the standard transfer potential of X^-, which is *ca.* −185 mV.

The physicochemical parameters derived from the voltammograms are given in *Table 1*, where the pK_a values of cetirizine are recalled.

Hydroxyzine. Representative voltammograms for the transfer of hydroxyzine at the 1,2-dichloroethane/H_2O interface are shown in *Fig. 3*.

1) Below pH 1.75, only one peak appears, with a peak-to-peak separation of nearly 60 mV. The half-wave potential becomes more negative when the aqueous pH increases. This wave represents the transfer of BH_2^{2+} (w), which crosses the interface by

Table 1. *Physicochemical Parameters of Cetirizine*

Parameter	Value
pK_{a1}	2.19 [6]
pK_{a2}	2.93 (COOH group) [6]
pK_{a3}	8.00 [6]
$\Delta_o^w\phi^0_{XH_2^+}$	-40 ± 8 mV
$\Delta G^{0,w\to o}_{t,XH_2^+}$	-3.9 ± 0.8 kJ · mol^{-1}
$\Delta_o^w\phi^0_{XH_3^{2+}}$	9 ± 5 mV
$\Delta G^{0,w\to o}_{t,XH_3^{2+}}$	-1.7 ± 1.1 kJ · mol^{-1}
$\Delta_o^w\phi^0_{X^-}$	*ca.* -185 mV
$\Delta G^{0,w\to o}_{t,X^-}$	*ca.* 17.8 kJ · mol^{-1}

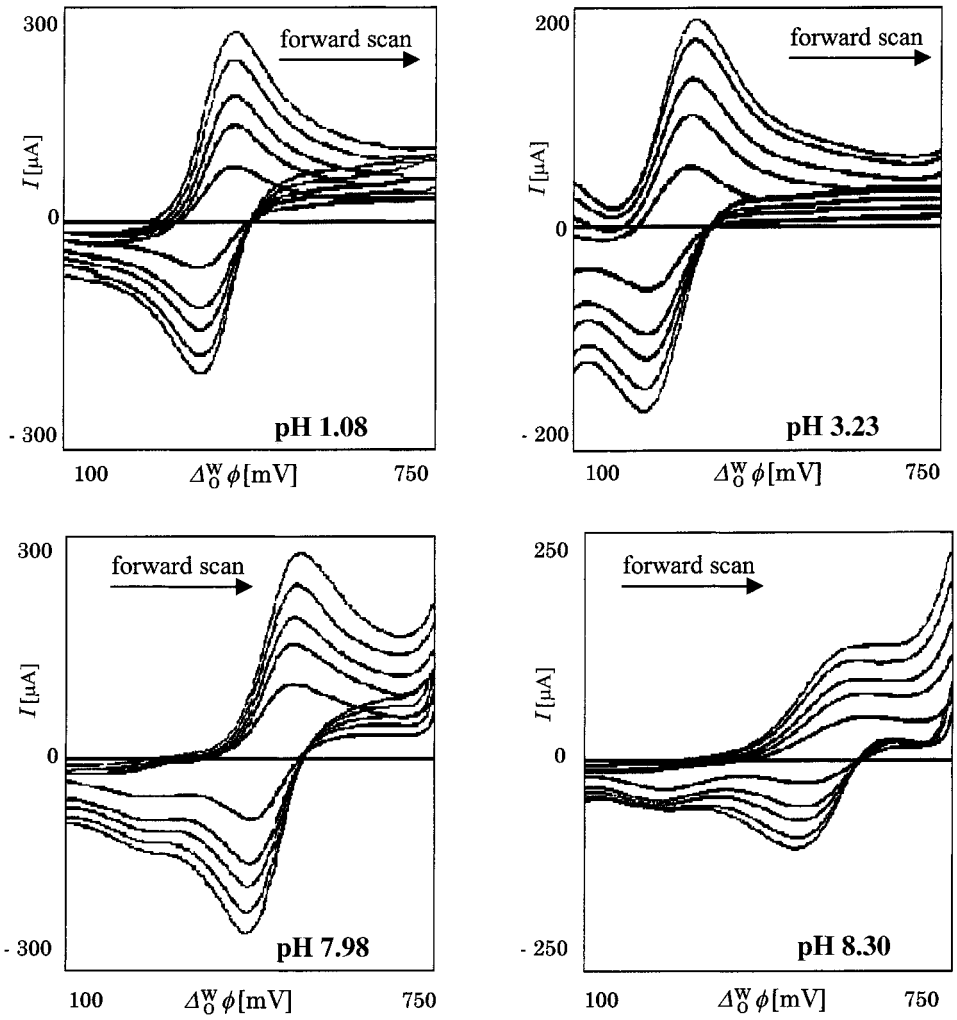


Fig. 3. *Representative cyclic voltammograms of hydroxyzine.* At each pH, potential scan rates are 30, 50, 80, and 100 mV/s.

losing one proton. As the pK_{a1} value of the couple $BH_2^{2+}/BH+$ is quite low ($pK_{a1} = 1.75$), neither the direct transfer of BH_2^{2+} across the interface nor the transfer of H^+ facilitated by $BH^+(o)$ are detectable.

2) Between pH 1.75 and pH 7.49, the wave of BH_2^{2+} is no longer visible, but a new peak appears, which is due to the transfer of BH^+ from H_2O to 1,2-dichloroethane. It allows the standard potential of transfer of BH^+ to be calculated (see *Table 2*).

3) Above pH 7.49, only one wave is observed, which is due to the assisted transfer of a proton by B(o) from H_2O to 1,2-dichloroethane.

The physicochemical parameters derived from the voltammograms are given in *Table 2*.

Table 2. *Physicochemical Parameters of the Ionized Forms of Hydroxyzine*

Parameter	Value
pK_{a1}	1.75 [6]
pK_{a2}	7.49 [6]
$\Delta_o^w\phi^0_{BH^+}$	-78 ± 15 mV
$\Delta G^{0,w\to o}_{t,BH^+}$	-7.2 ± 1.8 kJ · mol^{-1}

4.2. *pH-Dependent Lipophilicity Profiles of Cetirizine and Hydroxyzine.* The partition coefficients of the neutral forms of cetirizine and hydroxyzine were determined in the 1,2-dichloroethane/H_2O system by the pH-metric method. The surfactant ability of cetirizine led us to work with small solute concentrations and little volumes of 1,2-dichloroethane in order to minimize emulsion problems at high pH values. The large value of the tautomeric equilibrium constant between the zwitterionic and the non-charged species (K_Z) of cetirizine allows attribution of the $\log P^{XH}_{dce}$ measured by potentiometry to the zwitterionic form of the molecule.

The partition coefficients of the ionized forms of cetirizine and hydroxyzine were deduced from voltammograms by the determination of their half-wave potential and the use of *Eqns. 1, 2,* and *4*. Only the final results are summarized in *Tables 3* and *4*. The physicochemical parameters of anionic cetirizine are only indicative, since its tensioactive ability renders cyclic voltammetry measurements very difficult (see above).

The lipophilicity profiles of cetirizine and hydroxyzine in the 1,2-dichloroethane/H_2O systems (calculated from values in *Tables 3* and *4*) are compared in *Fig. 4*. They are similar to profiles observed in the octanol/H_2O systems [23] and show that the

Table 3. *Partition Coefficients of Cetirizine in 1,2-Dichloroethane/H_2O System*

Parameter	Value
$\log P^{XH}_{dce}$	0.74 ± 0.10
$\log P^{0,XH_2^+}_{dce}$	0.68 ± 0.14
$\log P^{0,XH_3^{2+}}_{dce}$	-0.30 ± 0.20
$\log P^{0,X^-}_{dce}$	*ca.* -3.13
diff ($\log P^{XH\text{-}XH_2^+}_{dce}$)	0.06
diff ($\log P^{XH\text{-}XH_3^{2+}}_{dce}$)	1.04
diff ($\log P^{XH\text{-}X^-}_{dce}$)	*ca.* -3.87

Table 4. *Partition Coefficients of Hydroxyzine in 1,2-Dichloroethane/H_2O system*

Parameter	Value
$\log P^{B}_{dce}$	3.57 ± 0.06
$\log P^{0,BH^+}_{dce}$	1.33 ± 0.24
$\log P^{0,BH_2^{2+}}_{dce}$	Non measurable
diff ($\log P^{B\text{-}BH^+}_{dce}$)	2.24

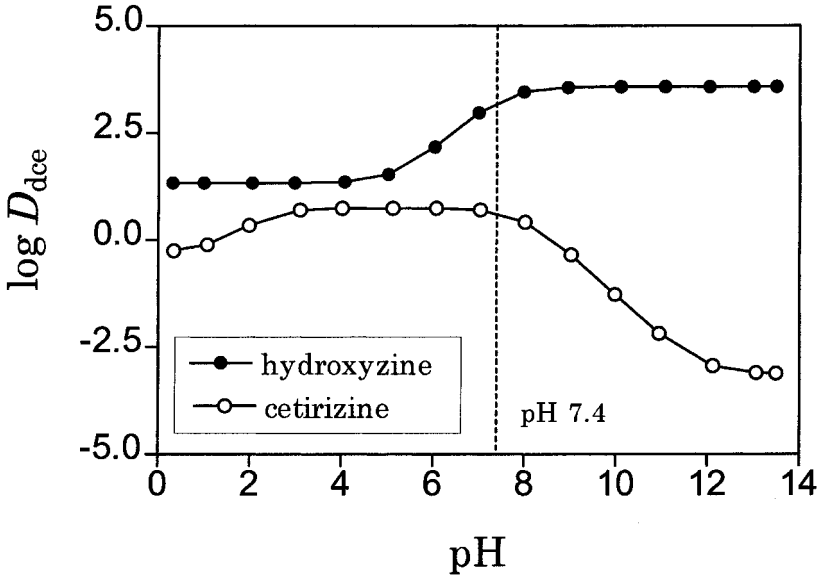


Fig. 4. *Lipophilicity profiles of cetirizine and hydroxyzine in the 1,2-dichloroethane/H_2O system, calculated from values in* Tables 1 *and* 2

distribution behavior of hydroxyzine is very different from that of cetirizine. Indeed, the former exists under physiological conditions as mixtures of a moderately lipophilic cation and highly lipophilic neutral form, whereas cetirizine exists in the 1,2-dichloroethane/H_2O systems practically exclusively as a zwitterion of moderate lipophilicity over a broad pH range (2.92 – 8.00) including the physiological value.

4.3. *Structural Effects on the Lipophilicity of Cetirizine and Hydroxyzine.* As in the octanol/H_2O system, the partition coefficient of zwitterionic cetirizine in the 1,2-dichloroethane/H_2O system ($\log P^{XH}_{dce} = 0.74$) is higher than the values commonly measured for zwitterions, suggesting that conformational effects lower the polarity of this electrical species. Quenched molecular dynamics (QMD) applied to zwitterionic cetirizine generated 52 conformers, which were classified by cluster analysis (whose results are presented in [9]). This study shows the presence of three main clusters of folded conformers, plus an isolated conformer, which is the only extended one and is energetically unfavorable in the vacuum. For all folded conformations, the distances between the proton at the N-atom and the two O-atoms are small enough to allow partial neutralization of the two charges of the zwitterion (see *Fig. 5, a*).

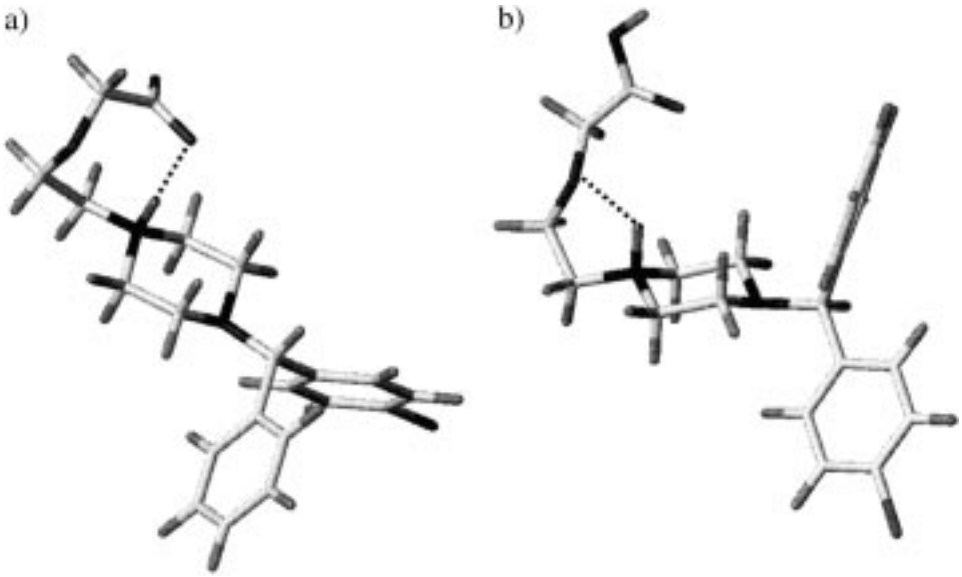


Fig. 5. a) *Zwitterionic cetirizine: low-energy folded conformation.* b) *Monocationic cetirizine: low-energy folded conformation.*

Since, in 1,2-dichloroethane/H_2O, monocharged species are usually 5 units less lipophilic than the uncharged one [24], the small difference (*diff* (log $P_{dce}^{XH\text{-}XH_2^+}$) observed for cetirizine indicates clearly an additional stabilization of the monocationic species in 1,2-dichloroethane (see *Table 3*). Here again, as indicated by molecular-dynamics simulations, the most stable conformers of the monocation have the ether O-atom close enough to the H-atom of the protonated N-atom to form an intramolecular H-bond (*Fig. 5, b*). In contrast, *diff* (log $P_{dce}^{XH\text{-}X^-}$) is near 4 and reveals that the negative charge in anionic cetirizine is localized on the carboxyl group.

Strong H-bond donors like hydroxyzine, alcohols, and carboxylic acids are generally less lipophilic in 1,2-dichloroethane/H_2O than in octanol/H_2O and are characterized by a large positive value of the difference (Δlog $P_{oct\text{-}dce}^{B}$ [25]. However, the Δlog $P_{oct\text{-}dce}^{B}$ of +0.07 measured for hydroxyzine suggests an intramolecular H-bond between the OH group and one of the N-atoms of the piperazine ring in the neutral form of hydroxyzine.

A *diff* (log $P_{dce}^{B\text{-}BH^+}$) value of 2.24 was found for hydroxyzine (*Table 4*). As for cetirizine, this small difference indicates clearly an additional stabilization of monocationic hydroxyzine. Intramolecular interactions are responsible for this enhancement of lipophilicity, since the most-stable conformers of monocationic hydroxyzine calculated by QMD are folded by H-bond interactions between the protonated N-atom and the OH or the ether O-atoms.

When hydroxyzine is diprotonated, its solvation in 1,2-dichloroethane is less favorable as each N-atom has its own proton, and the charges are now much more localized. However, the low pK_{a1} value prevents the partition coefficient of the dicationic species to be measured by cyclic voltammetry.

The measurements in the 1,2-dichloroethane/H_2O system confirm that strong conformational effects act on the partitioning of the different electrical species of cetirizine and hydroxyzine, and may influence their pharmacokinetic behavior.

4.4. *Ionic Partition Diagrams.* As explained in the theoretical part, the partitioning behavior of an ionized drug is not only pH-dependent, but also potential-dependent. Thus, the presence of one species in a given phase depends directly on the aqueous pH and on the difference of potential existing across the interface. The later is the *Galvani* potential difference $\Delta_o^w\phi$ and depends on the concentration, the activity coefficients, and the lipophilicity of all ions in the system, as well as on the volume of each phase and on the temperature [13][26]. To better understand the partition of ionized cetirizine and hydroxyzine across the interface, ionic partition diagrams at 25° were drawn for each drug according to principles developed in [27] and on the basis of the ionization constants and standard transfer potentials in *Tables 1* and *2*. Ionic partition diagrams represent the domain of predominance of the species as a function of $\Delta_o^w\phi$ and aqueous pH, and they allow a direct interpretation of the mechanisms governing the transfer of the various electrical species.

The ionic partition diagram of cetirizine is presented in *Fig. 6* and shows the good agreement between experimental results and theory. A more detailed ionic partition diagram for the low pH range is presented in *Fig. 7*. The seven theoretical lines represent equiconcentration domains of two adjacent species [28]. They separate the diagram in five domains of predominance of each electrical state of cetirizine, numbered from 1 to 5.

At very low pH, XH_3^{2+} is the predominant electrical species. Boundary line **a** represents the standard transfer potential of XH_3^{2+} ($\Delta_o^w\phi^0_{XH_3^{2+}}$). When, at this pH, the

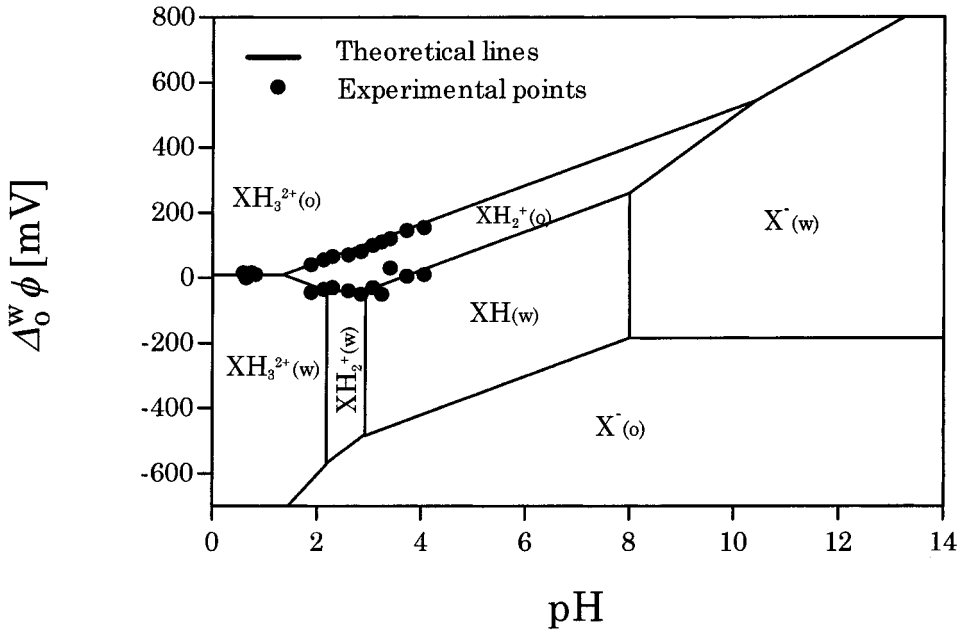


Fig. 6. *Ionic partition diagram for cetirizine in 1,2-dichloroethane/H_2O system at 25°*

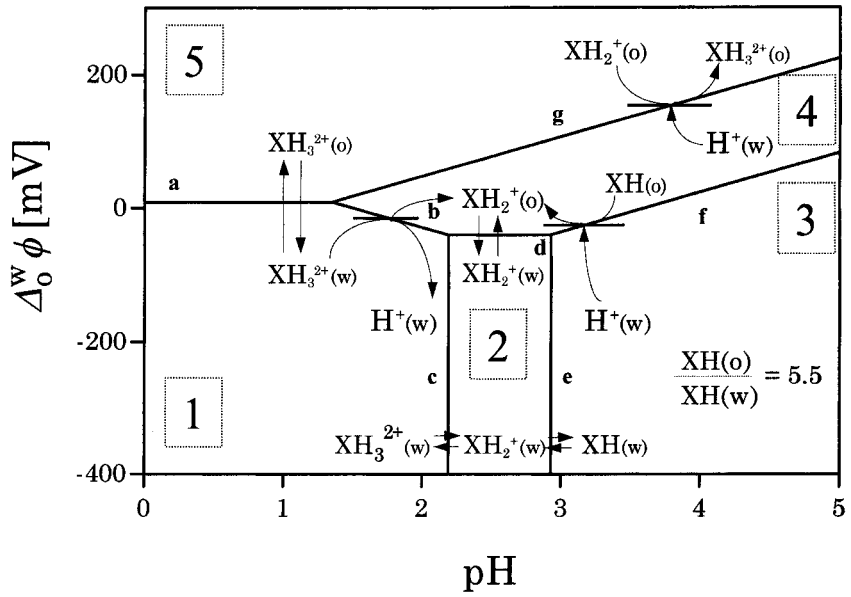


Fig. 7. *Schematic transfer mechanisms of the various electrical forms of cetirizine at the 1,2-dichloroethane/H_2O interface at 25°.* Lines **a**, **b**, **c**, **d**, **e**, **f**, and **g** are theoretical lines that delimit the different domains of predominance of each electrical species, numbered from 1 to 5.

Galvani potential difference between the two phases, $\Delta_o^w\phi$, is lower than $\Delta_o^w\phi^0_{XH_3^{2+}}$, then most of diprotonated cetirizine is in the aqueous phase (domain 1). In contrast, if $\Delta_o^w\phi$ is higher than $\Delta_o^w\phi^0_{XH_3^{2+}}$, the greater part of diprotonated cetirizine is in the organic phase (domain 5). The shape of voltammograms described above indicates that XH_3^{2+} can cross the interface by a direct transfer from H_2O to 1,2-dichloroethane. In the pH zone limited by boundary lines **c** and **e** (*i.e.*, for $pK_{a1} \leq pH \leq pK_{a2}$) similar considerations apply to XH_2^+.

At higher pH, the presence of XH_2^+ requires more detailed considerations. Line **b** represents the *Galvani* potential differences for which the concentrations of XH_2^+ in the aqueous phase and of XH_3^{2+} in the organic phase are equal. The greater part of cetirizine exists as a dication in the aqueous phase when $\Delta_o^w\phi$ is below line **b**, whereas it is as a monocation in the organic phase if $\Delta_o^w\phi$ is above line **b** and below line **g** (domain 4). Line **b** shows that dicationic cetirizine in the aqueous phase must lose a proton to cross the interface. In the same way, when $\Delta_o^w\phi$ increases, monocationic cetirizine in the organic phase recovers its second proton from the aqueous phase (line **g**) and acts as a proton ionophore.

In domain 3, the predominant species is zwitterionic cetirizine. At physiological pH, in particular, it can also act as proton acceptor to produce the monocharged species in the organic phase (line **f**).

The part of the ionic partition diagram corresponding to high pH and including transfer of anionic cetirizine is not described in this paper, considering the experimental difficulties encountered. More details on the mechanisms of transfer of anions are given in [26].

As the standard transfer potential of BH_2^{2+} cannot be measured, it is not possible to draw the complete ionic partition diagram of hydroxyzine. Hence, the diagram presented in *Fig. 8* gives only a partial view of the mechanism of transfer of hydroxyzine. Only the transfer of BH_2^{2+} by interfacial dissociation (low pH) and the transfer of a proton assisted by B (high pH) could be drawn.

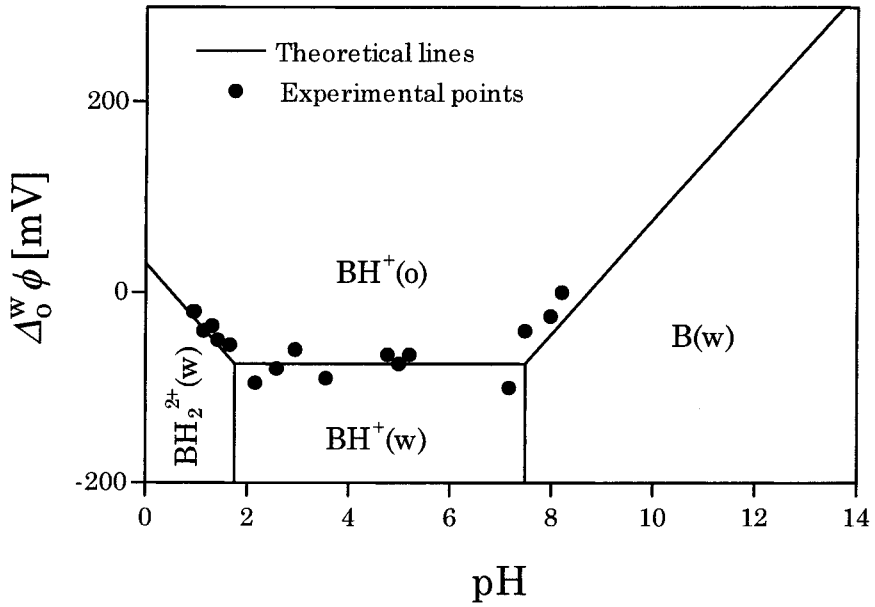


Fig. 8. *Ionic partition diagram for hydroxyzine in the 1,2-dichloroethane/H_2O system*

5. Conclusion. – This study confirms the importance of conformational effects on the partition properties of cetirizine and hydroxyzine, with obvious pharmacokinetic implications. Moreover, the ionic partition diagram of cetirizine underlines the complexity of the interfacial mechanisms of transfer. In particular, cetirizine can facilitate proton transfer, a property of biological relevance [29][30].

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