A Cellular Automata Model of Acid Dissociation

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A dynamic cellular automata model that simulates the dissociation of an organic acid in solution is described. In the model, acids are represented by a novel cell type in which one face corresponds to the dissociating carboxylic acid group and the remaining faces represent the anionic portion of the acid. Simulations are described that analyze the effects of variable acid strength, changes of solvent temperature, and environmental influences, such as the presence of cosolutes and other acids. Several general features of acid dissociation in solution are replicated by the model and some additional aspects are examined. As a rule, additional solutes depress acid dissociation, the effect being greatest when the added cosolute is lipophilic, as might occur, for example, in a biological system. In mixtures of two different acids, the dissociation of each is suppressed, the weaker acid experiencing the greater suppression.

INTRODUCTION

Dissociation of an organic acid in solution is one of the most important processes in chemical and biological systems. The tendency of the anion—hydrogen bond to break in this dissociation is customarily characterized by its ionization constant K_a, or alternatively, by the negative logarithm of K_a, the pK_a value. Some of the molecular structural features influencing this dissociation are fairly well understood[1−3] and can be described theoretically by quantum chemical calculations[4] or estimated by empirical relationships such as the Hammet equation.

Acid dissociation is a function of the environment of the acid molecule as well as its structure. In this context, "environment" includes factors such as the temperature and the presence of other solutes and dissociating species. The influences of these environmental features are less well understood, but are of special interest in biological systems. The dissociation state of a carboxylic acid group within an enzyme active site, for example, may be crucial to substrate binding, and changes in this as binding occurs may be influential in the catalytic mechanisms. The pK_a of a glutamic acid or aspartic acid residue in a protein may differ from the dilute solution pK_a of a simple non-protein equivalent acid by as much as 3 pK units because of its particular environment in the protein.[6]

Over the past four years we have employed cellular automata models to examine a variety of liquid-phase properties[7,8] and related phenomena, such as micelle formation,[9] first-order kinetics,[10] and enzyme kinetics.[11] In the present studies we explore some aspects of the dissociation of an organic acid through simulations using a cellular automata model.

THE CELLULAR AUTOMATA MODEL

Cellular automata were first introduced by von Neumann over 50 years ago.[12] In modern realization these automata are digital computer programs that simulate dynamic events on a checkerboard field consisting of $nxm = N$ cells. Each cell can exist in a number of different *states,* which may, in chemical applications, represent different chemical species, or different conditions of a single species. Active cells can (i) move to adjacent unoccupied positions in the field and (ii) change their states subject to certain rules. The movement and state transformation rules, which may be fixed or probabilistic, determine—or in the case of probabilistic rules, "guide"—the subsequent evolution of the system from its initial condition. By their nature, cellular automata systems are discrete in space (cells), time (iterations), and state (colors). This discreteness is in contrast to the common approach to physical problems wherein coupled differential equations are applied to systems in which time and space are continuous and only the states are discrete.

Our cellular automata approach to physicochemical phenomena has been described in some detail in earlier papers,[7−11] but here we give a brief summary. We have developed a computer program (DING-HAO)[13] that simulates dynamic processes and monitors the developing attributes of an *nxm* system of cells. Different states of the cells are

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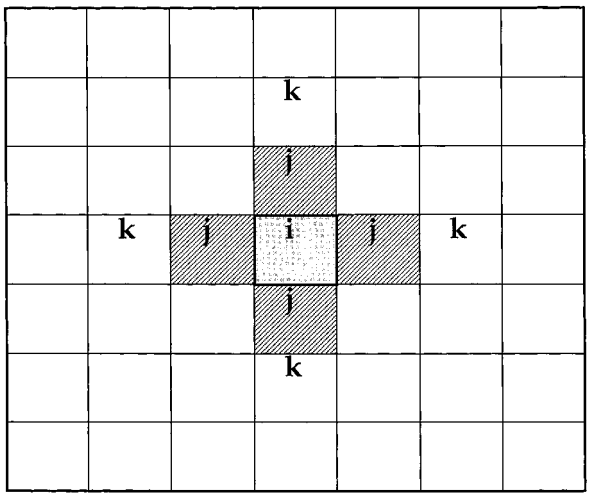

Figure 1. The von Neumann neighborhood of a cell. The *k* cells comprise the extended von Neumann neighborhood of cell i.

represented by different colors, and the movement and state transition rules are probabilistic. Each system evolves from its initial condition via time-step iterations in which every cell is interrogated in random order and given an opportunity to move to an adjacent unoccupied position in the field.

In the applications to be described, two parameters have been selected to govern the movement probabilities. The von Neumann neighborhood of a cell is pictured in Figure 1. The *breaking probability* $P_B(X,Y)$ is the probability that a cell X in location *i* of Figure 1 will detach from a cell Y in an adjacent *j* cell when there is exactly one such occupied *j* cell. The value of $P_B(X,Y)$ is adjusted for additional Y cell, but is always less than or equal to unity. When X and Y are of the same type, this probability is denoted by $P_B(X)$ or $P_B(Y)$, as in earlier studies.

The *joining probability* $J(X,Y)$ describes the movement of an X species in cell *i* toward or away from a Y in cell *k* of the extended von Neumann neighborhood when the intervening *j* cell is vacant. The probability $J(X,Y)$ represents the ratio of the probability that the X cell in *i* will move toward a *k* cell when the *k* cell is occupied by Y to the movement probability when the *k* cell is vacant. The parameter *J* is a positive number. When $J(X,Y) = 1$, the X species in cell *i* has the same probability of movement toward an occupied *k* cell as when cell *k* is empty. When $J(X,Y) > 1$, the X species in *i* has a greater probability of movement toward an occupied *k* cell than when cell *k* is empty. When $J(X,Y) < 1$, the X cell has lower probability of such movement. When X and Y are the same, this probability is denoted by $J(X)$ or $J(Y)$.

The solvent "water" cells (W) in this study were characterized by the same parameters as in earlier studies [i.e., $P_B(W) = T(°C)/100$ and $J(W) = 1$]. The cells representing the acids as well as their dissociation products, anion and hydronium ion, required a more complicated treatment, as will be described next.

The Acid Cells. The acid cells were structured in a manner similar to that used for the cells in an earlier study of micelle behavior.[9] In the present case, one of the four cell faces (Y) was designated as representing the carboxylic acid group, whereas the other three faces (X) were regarded as more lipophilic and comprising the remainder of the acid. The XY species move throughout the system as in the micelle

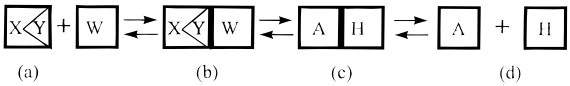

Figure 2. The general scheme employed for acid dissociation: an acid cell XY encounters a water cell W and dissociates to form an hydronium ion H and an anion A.

study, and are subjected to rotation to a different orientation of the faces with probability of 0.25 per iteration. Figure 2 pictures such a cell and the sequence of events leading to dissociation in the present simulation. These events simulate intermediate stages of the following dissociation process:

$$\underset{(a)}{RCOOH} + H_2O \rightleftharpoons \underset{(d)}{RCOO^- + H_3O^+}$$

When the XY species encounters a W cell at its Y face, a complex XY−W forms. The transition (b) → (c) in Figure 2, from XY−W to A−H, is regarded as the "dissociative" event for purposes of the simulation and assigned a (generally low) probability P_D. In stage (c) → (d), the anion A and hydronium ion H separate.

Breaking and joining probabilities were selected to reflect the general lipophilicity or hydrophilicity of the species involved. For example, the Y face and the species A and H were regarded as hydrophilic and assigned relatively low P_B values with respect to water cells W. In contrast, the X faces of the XY cells were assigned rather high P_B values with respect to water.

It is well known that the mobilities of H^+ and OH^- ions in aqueous solution are considerably greater than those of other ions due to "proton hopping" between water molecules. To account for this phenomenon, the hydronium ions were allowed to transfer their character to adjacent W cells (as the water cells were interrogated during an iteration) via an exchange interaction HW → WH with unit probability per iteration. This resulted in a greater-than-normal mobility for the H species. As H and A moved throughout the grid they occasionally encountered one another and could reassociate as A−H pairs, potentially leading to undissociated XY−W pairs in the reverse of the (b) → (c) step. Certain other associations were prohibited in the simulations by assigning low or zero breaking, joining, or transition probabilities: for example, the encounter of a Y (-COOH) face of the XY acid with an hydronium ion H was rendered ineffective by assigning a low joining probability. Encounters between hydronium ions and added solutes were also parameterized to reflect a low probability of reaction. The standard parameters employed are summarized in Table 1. Parameters not in this list are specifically defined under each study.

All studies were carried out using a $70 \times 70 = 4900$ cell grid. As in our earlier work, ~31% of the cells were left unoccupied to simulate the free space of water. Thus, 3400 water cells were used as a starting concentration; when acid and other cell species were introduced, these new cells replaced water cells in the simulations.

RESULTS

Five studies were conducted to examine separate aspects of acid dissociation under the influence of various factors.

Study 1: Acid Strength. The objective of this first study was to examine the dissociation of an acid in solution with

Table 1. Standard Parameters Used in the Cellular Automata Simulations[a]

interaction	breaking probability	joining probability
X−X	0.5	0.5
X−Y	0.8	0.3
Y−Y	0.3	0.8
X−W	0.8	0.3
X−H	0.9	0.25
X−A	0.8	0.3
Y−W	0.3	0.8
Y−H	0.2	1.0
Y−A	0.3	0.8
W−H	0.25	1.0
W−A	0.6	0.4
H−H	1.0	0.0
H−A	0.5	0.5
A−A	0.7	0.35

[a] X refers to the nonpolar faces of the acid cell, Y is the carboxylic acid face of the acid cell.

Table 2. Dependence of the Dissociation Constant and pH on the Intrinsic Acid Dissociation Parameter P_D

P_D	α	K_a	pH
0.05	0.22	0.0514	0.66
0.10	0.31	0.115	0.56
0.15	0.37	0.180	0.50
0.25	0.43	0.268	0.45
0.50	0.54	0.526	0.36

emphasis on the acid strength, to establish a framework for subsequent studies. The intrinsic acid strength was modeled through the probability P_D of the dissociation process (b) → (c) in Figure 1, as already described. This probability was varied, and the resulting species concentration noted once "equilibrium" was established.

The conditions for the interactions of the species involved were selected to fall in the mid-range of probabilities, as indicated from previous studies. A temperature of 25 °C was simulated by setting the water breaking probability P_B-(W) to 0.25. Fifty acid cells were placed in random locations on the grid, along with 3350 water cells. Based on the molarity of pure water of 55.55 M, this represents an approximate concentration of $c_0 = (50/3350)55.55 = 0.83$ M. This value is higher than desirable, but one necessitated by the conditions of the simulation. The "lipophilicity" of the anion faces of the acid cells was set at an intermediate value by setting P_B(X,W) to 0.50. For simplicity the "concentrations" of the species were often expressed as simple cell counts. Simulations were allowed to run until a relatively constant hydronium ion concentration [H] was established, a condition that was found to prevail at times ≥1000 iterations. The fractional dissociation was determined as $\alpha = [H]/[XY]_o$, and the acid dissociation constant K_a calculated as:

$$K_a = c_0\,\alpha^2/(1-\alpha^2)$$

Ten simulations for each P_D condition were run and averaged. The results for the fractional dissociation and K_a values as a function of P_D are shown in Table 2. As anticipated, an increase in P_D increases both α and K_a in a regular manner. Although predictable, this result sets a control condition for later, more complicated simulations.

Study 2: Effect of Acid Concentration. The objective of the second study was to examine the effect of a change in the starting acid concentration $[XY]_0$ on the dissociation of the acid. Of particular interest was the variation of K_a with acid concentration. Three starting concentrations were examined, namely $[XY]_0 = 50$, 100, and 150 acid cells. As before, added acid cells displaced water cells, keeping the total occupied cell count at 3400. Ten simulation runs of 1000 iterations were carried out, and the averages from these employed for analysis.

Table 3. Effect of Initial Acid Concentration (Expressed as Counts of Cells) On the Dissociation Constant K_a

$[XY]_0$	α	K_a	pH
50 cells	0.22	0.051	0.66
100 cells	0.16	0.051	0.55
150 cells	0.13	0.050	0.48

Table 4. Effect of Water Temperature on the Dissociation of the Acid

water temperature (°C)	α	K_a
10	0.24	0.063
25	0.22	0.051
50	0.18	0.033
75	0.17	0.017

The equilibrium count of the hydronium ion cells [H] was determined for each acid concentration and employed to determine the dissociation fraction α, with the results shown in Table 3. (The variation in [H] for these and similar runs was ∼2%.) The results reveal that K_a remains approximately constant as the "concentration" of the acid is changed within the range examined.

Study 3. Effect of Water Temperature on the Acid Dissociation. A special advantage of the cellular automata model is that it allows examination of the influences of individual environmental features in isolation from other variations that might normally occur simultaneously and thereby cloud the understanding of the relative roles of these independent effects. In the present study, the influence of water temperature on the acid dissociation was examined in isolation from other features, such as, for example, an increase in the tendency of the acid itself to dissociate, which might also occur as the temperature is raised. This study thus begins evaluation of the influences of environmental conditions on the dissociation of the acid in solution.

Four temperatures were chosen to evaluate the extent of acid dissociation. As in earlier studies, water temperature was simulated by setting the water breaking probability P_B-(W) = T(°C)/100. All other parameters were held constant. As before, 50 acid cells were introduced, with 3350 water cells. Ten simulations of 1600 iterations each were run, and the average dissociation obtained at each temperature. The results are shown in Table 4. With the parameters employed, an increase in water temperature produces a decrease in the acid dissociation constant K_a, as reflected in the decline of α at equilibrium. The observed decrease in K_a is in agreement with the common (but far from universal) observation that the dissociation constants of organic acids often decrease at elevated temperatures.[14]

Study 4. Effect of Co-Solute Lipophilicity. The objective of this investigation was to examine the effect of a second, nondissociating solute (cosolute) on the dissociation of the acid cells. This objective is of interest because it may be relevant to the study of more complex conditions, such as those that might prevail in biological media.

Table 5. Effect of Cosolute Lipophilicity on the Acid Dissociation

relative lipophilicity[a]	[H][b]	α	K_a
no cosolute	15.5	0.310	0.115
0.25	15.3	0.306	0.117
0.50	14.5	0.290	0.103
0.90	13.9	0.278	0.093

[a] High values signify relatively nonpolar, lipophilic cells. [b] Average cell counts at equilibrium, with standard deviation of 0.3.

Table 6. Results for Simulations of Two Acids

	isolated		mixture 1		mixture 2	
parameter	acid 1	acid 2	acid 1	acid 2	acid 1	acid 2
$[A_i]_0$	100	100	50	50	100	100
$[H]_{tot}$	17.5	28.5	22.6		33.4	
α	0.175	0.285	0.126	0.326	0.093	0.241
K_a	0.0625	0.191	0.0153	0.133	0.0166	0.133

The system was constructed using 50 acid cells and 150 cosolute cells of varying lipophilicity. For this study, the inherent dissociation probability P_D of the acid was taken to be 0.10. The relative lipophilicity of the cosolute was modeled using rules governing the probability $P_B(W,S)$ of cosolute/water breaking: the higher this probability, the greater the lipophilicity of the cosolute. The other rules were held constant.

Three values of the cosolute lipophilicity were tested, along with a control condition in which no cosolute was present. The hydronium ion concentrations [H], expressed as cell counts at equilibrium, were averaged for 10 runs and are shown in Table 5. Also shown in Table 5 are the acid dissociation constants under these conditions. The simulations indicate that the presence of cosolutes leads to a small decrease in the dissociation of the acid cells, and the extent of this decrease increases with increased lipophilicity of the cosolute. For relatively hydrophilic cosolutes, the effect on K_a is very small and not statistically significant.

Study 5. Interaction of Two Acids. In this study it was of interest to examine the dynamics of two acids interacting in solution. The two acids were designated A1 and A2 and assigned different dissociation probabilities, P_D: Acid 1 was assigned $P_D = 0.05$ and Acid 2 was assigned $P_D = 0.15$. The latter is therefore the stronger acid.

As a control measure it was necessary to examine each acid in isolation. For this pupose, a 4900-cell grid containing 3300 water cells was used, with either 100 A1 or 100 A2 cells. Each acid was examined by simulation to determine its dissociation constant, and average equilibrium cell counts from 10 runs were determined. The dissociation fraction here was determined as $\alpha_i = [A_i]/[\text{Acid}]_0$. The results are shown in Table 6. It is apparent that, as expected, the relative strengths of the acids are reflected in their equilibrium [H] counts and fractional dissociations α: Acid 2, the stronger acid, has higher [A], [H], and α values.

Next, equal concentrations of the two acids were placed in solution together to assess any mutual influences that might arise. This assessment required the introduction of additional rules to account for the dynamics of anion−anion interactions and also undissociated acid−anion encounters. To minimize the complications possible here the same probabilities were adopted for these cross-terms as were used for identical cells.

Two sets of simulations were used, one with 50 cells of each acid type and the second with 100 cells of each. The simulations were allowed to proceed until relatively constant values for [H], [A1], and [A2] were obtained. Dissociations of the two acids were monitored with the anion counts [A1] and [A2]. For each simulation, 20 runs were taken and averaged, and the results are shown in Table 6.

The mixtures demonstrate a strong and unequal influence of a second acid on the dissociation of the two acids. In Mixture 1, in which both acids are present at half their original concentrations used in the isolated simulations, Acid 2 shows the greater dissociation expected as a result of its lower concentration. However, the dissociation of Acid 1 is notably depressed by the presence of the second, stronger, acid. The "common ion effect" of the hydronium ion [H] is even more apparent in the results for Mixture 2, where both acids are present at their original strengths. The dissociations of both acids are suppressed from their isolated values, dissociation of the weaker acid A1 being significantly more suppressed than that of the stronger acid A2.

DISCUSSION

The results demonstrate that the cellular automata models described are capable of replicating several general features of the dissociation of organic acids in solution. In the first study, variation of the acid strength (i.e., breaking) probability P_D, which reflects the ease of ionization of the acid group due to inherent structural features, was seen to lead, as expected, to greater fractional ionization α, higher K_a, and lower pH. In the second study, the dissociation constant K_a remained approximately constant, as desired, as the acid concentration was varied over a modest range.

In the third study, a single environmental feature, the "temperature" of the water solvent, as embodied in the water−water breaking probability $P_B(W)$, was varied with the result that the dissociation of the acid decreased. It is interesting that this decrease occurred despite holding the inherent acid dissociation probability P_D constant. The observed decrease is, moreover, consistent with the observation that polar solvents such as water become less polar as temperature increases (as evidenced, for example, by decreasing dielectric constant), and therefore less hospitable to ionic species such as the hydronium ion and anion of the acid. (The temperature variation of solvent character has a fairly dramatic illustration in the experimental observation of thermochromic color changes exhibited by various dyes, such as the rhodamines.) Clearly, the actual dissociation behavior of an organic acid with temperature is a more complicated matter than described here, encompassing at the very least variation of both P_D and $P_B(W)$. However, an important strength of the cellular automata approach is its ability to separate the influences of concurrent environmental and inherent factors.

The fourth study suggests that the presence of lipophilic cosolutes may alter the dissociation of organic acid groups. This study and the previous one imply that the dissociation of acid groups should be suppressed in a lipophilic environment of the type experienced, e.g., in enzymes and biological systems.

The fifth study examines the consequences of mixing two acids of unequal strength. It is apparent that, although each

acid suppresses the dissociation of the other, the stronger acid dissociates largely at the expense of the weaker acid. The decrease in dissociation of two acids in a mixture cannot be simply and directly calculated from the concentrations of the acids and their dissociation constants in pure solution because of the complicating influences of ionic solvation effects on the water structure, and the dependences of both of these factors on temperature.[15]

Changes in the pK_as of acid groups can be calculated by free energy perturbation methods and are directly related to electrostatic contributions to molecular stability and binding. The standard approach is to assume an intrinsic pK_a for the isolated acid and to calculate the shift in pK_a resulting from its presence in a defined environment. For example, the pK_a shifts of ionizable groups "buried" in proteins result from both polar and nonpolar influences. These influences can be calculated, but the calculations are not at all simple or direct.

In contrast, the approach adopted here, although it does not directly address details at the atomic structural level or the influences of features such as solute size and shape, has advantages of simplicity, a relatively intuitive form, and computational accessibility. It appears that many of the environmental influences on acid dissociation behavior can be encapsulated in simple empirical rules such as the breaking and joining probabilities employed in these studies. The *effects* of these rules emerge naturally in the form of system attributes as the simulations proceed. Moreover, the rules can be varied singly to isolate the effects of individual factors on the phenomena in question.

As demonstrated in the foregoing studies, the attributes emerging from the models presented are either in accord with experimental observations or are intuitively reasonable where experimental evidence is lacking. The latter aspect illustrates the potential value of such dynamic simulations in uncovering aspects or phenomena that may have been previously unexplored or undiscovered. Cellular automata, through their simple, heuristic rules of interaction, offer an opportunity to explore easily and rapidly the consequences of variations in the interactions of species in complex systems. Such simulations therefore offer a new, attractive resource for analyzing and understanding the behaviors of such systems.

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