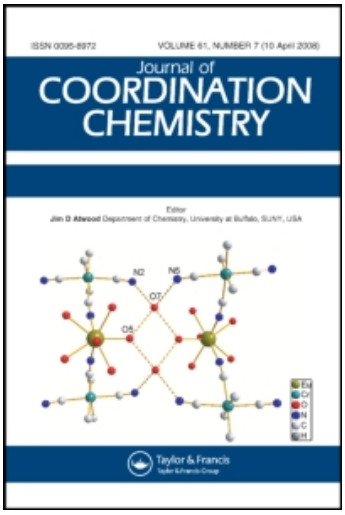

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Kinetics of base hydrolysis of α-amino acid esters catalyzed by $[Pd(Et_4en)(H_2O)_2]^{2+}$

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Kinetics of base hydrolysis of α-amino acid esters catalyzed by $[Pd(Et_4en)(H_2O)_2]^{2+}$

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The kinetics of base hydrolysis of amino acid esters, glycine-, histidine-, and methionine methyl esters in the presence of $[Pd(Et_4en))(H_2O)_2]^{2+}$ is studied in aqueous solution at 25°C and $I = 0.1\,mol\,dm^{-1}$ ($Et_4en = N,N,N',N'$-tetraethylethylenediamine). The rate of ester hydrolysis for glycine methyl ester is studied at different temperatures and dioxane–water solutions of different compositions. The kinetic data fit a model which assumes that hydrolysis proceeds in one step. Hydrolysis of the esters is catalyzed by $[Pd(Et_4en)(H_2O)_2]^{2+}$ with catalysis ratio values of 2.5×10^4, 3.15, and 7.43 for glycine-, histidine-, and methionine methyl esters, respectively. Activation parameters for the base hydrolysis are evaluated.

Keywords: Ester hydrolysis; Catalysis; pH-Stat

1. Introduction

Metal-ion promoted hydrolysis of amino acid esters has been the focus of increasing research [1–3], explored since 1952 [4–6]. Much work has been published [7, 8] on the hydrolysis of α-amino acid esters coordinated to metals such as cobalt(III), copper(II), and nickel(II). Such systems can be regarded as biomimetic models for certain metalloenzymes, as the metalloenzyme-substrate complex can be considered as a special type of mixed-ligand complex. However, little information is available on the palladium(II) systems.

Work in our laboratory [9–14] has focused on metal complex catalysis of the hydrolysis of various amino acid esters. The mixed ligand complex $[Pd(en)L]^{2+}$ undergoes hydrolysis by water and hydroxide ion [8]. It is therefore of considerable interest to extend this study to the mixed ligand complex with N,N,N',N'-tetraethylethylenediamine (Et_4en). The introduction of steric hindrance on the ethylenediamine ligand can be used to tune the reactivity of this metal center in possible catalytic and biological applications as in hydrolysis of the ester group.

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2. Experimental

2.1. *Materials and reagents*

All reagents were of Analar grade. $PdCl_2$ and Et_4en were provided by Aldrich. The glycine-, histidine-, and methionine methyl esters were purchased from Fluka. Carbonate-free NaOH was prepared and standardized against potassium hydrogen phthalate solution. All solutions were prepared in deionized H_2O.

$[Pd(Et_4en)Cl_2]$ was prepared by heating $PdCl_2$ (0.177 g, 1 mmol) in 40 mL H_2O and KCl (0.149 g, 2 mmol) to 70°C for 30 min. The clear solution of $[PdCl_4]^{2-}$ was cooled to 20°C and filtered, and Et_4en (0.172 g, 1 mmol) in 10 mL H_2O was added dropwise to the stirred solution. The pH was adjusted to 2–3 by addition of $HClO_4$. A yellow precipitate of $[Pd(Et_4en)Cl_2]$ was formed and stirred for another 2 h at 50°C. Afterwards, the precipitate was filtered off and washed sequentially with H_2O, ethanol and diethyl ether. A yellow powder was obtained. Anal. Calcd for $C_{12}H_{24}N_2PdCl_2$: C, 38.6; H, 6.4; and N, 7.5. Found: C, 38.5; H, 6.5; and N, 7.4. The IR spectrum of $Pd(Et_4en)Cl_2$ exhibits strong NH absorption in the range 3113–3207 cm^{-1}; δ (NH) bands are observed at 1580–1609 cm^{-1}. The Pd–N absorption was detected at 439 cm^{-1}. Aqueous solutions of the diaqua form of the $[Pd(Et_4en)Cl_2]$ complex were prepared *in situ* by addition of slightly less than two mole equivalents of $AgNO_3$ to a solution of a known amount of the dichloro complex and stirred overnight. The white precipitate of AgCl that formed was filtered off using a 0.1 μm pore membrane filter. Great care was taken to ensure that the resulting solution was free of Ag^+ ion and that the dichloro complex had been converted completely into the diaqua species. The ionic strength of the solutions was adjusted to 0.1 mol L^{-1} with $NaNO_3$ (Acros, p.a.).

2.2. *Apparatus and measuring techniques*

The kinetics of hydrolysis was monitored using a Metrohm 751 Titrino operated with the SET mode (titration to a preset end point). The titroprocessor and electrode were calibrated with standard buffer solutions according to National Institute of Standards and Technology (NIST) [15]. Hydrolysis kinetics of glycine-, methionine-, and histidine methyl esters in the presence of $[Pd(Et_4en)(H_2O)_2]^{2+}$ were investigated by pH-stat technique [7, 8], after equilibrating a solution mixture (40 cm^3) containing $[Pd(Et_4en)(H_2O)_2]^{2+}$ (2.5×10^{-3} mol L^{-1}), ester (2.5×10^{-3} mol L^{-1}), and $NaNO_3$ (0.1 mol L^{-1}) at the required temperature under nitrogen flow and the pH was brought to the desired value by the addition of 0.05 mol L^{-1} NaOH solution. The hydrolysis was then followed by the automatic addition of 0.05 mol L^{-1} NaOH solution to maintain the given pH constant. The data fitting was performed with the OLIS KINFIT set of programs [16] as described previously [17]. The precision of the kinetic data was estimated from a plot as obtained from the OLIS program output. The accepted residual values are less than 10^{-2}. Values of the hydroxide ion concentration were estimated from the pH using $pK_w = 13.997$ and an activity coefficient of 0.772 was determined from the Davies equation [18]. For variable temperature studies, the following values of pK_w and γ were employed [19], and at 15°C ($pK_w = 14.35$, $\gamma = 0.776$), at 20°C ($pK_w = 14.16$, $\gamma = 0.774$), at 25°C ($pK_w = 14.00$, $\gamma = 0.772$), at 30°C ($pK_w = 13.83$, $\gamma = 0.770$), at 35°C ($pK_w = 13.68$, $\gamma = 0.768$).

3. Results and discussion

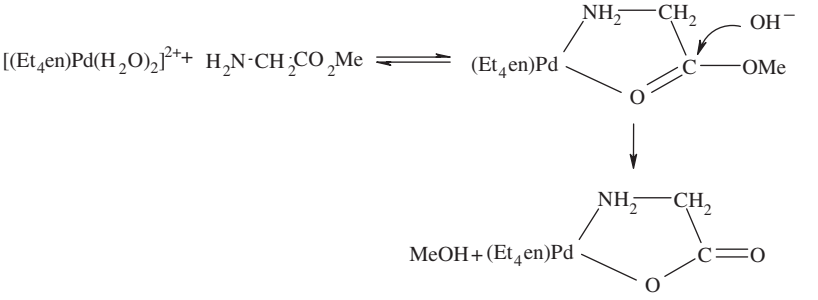
α-Amino acid esters react with $[Pd(Et_4en)(H_2O)_2]^{2+}$ according to equilibrium (1). The equilibrium constant is expected to be $\gg 1$ due to the high affinity of Pd^{II} to react with nitrogen donors [8]. The resulting $[Pd(Et_4en)L]^{2+}$ $[L = NH_2CH(R)CO_2R']$ undergo hydrolysis by water and hydroxide ion according to reactions (2) and (3), where $L' = NH_2CH(R)CO_2^-$.

$$\left[Pd(Et_4en)(H_2O)_2\right]^{2+} + L \underset{}{\overset{K}{\rightleftharpoons}} [Pd(Et_4en)L]^{2+} + 2H_2O \tag{1}$$

$$[Pd(Et_4en)L]^{2+} + H_2O \xrightarrow{k_{H_2O}} [Pd(Et_4en)L']^{+} + R'OH + H^+ \tag{2}$$

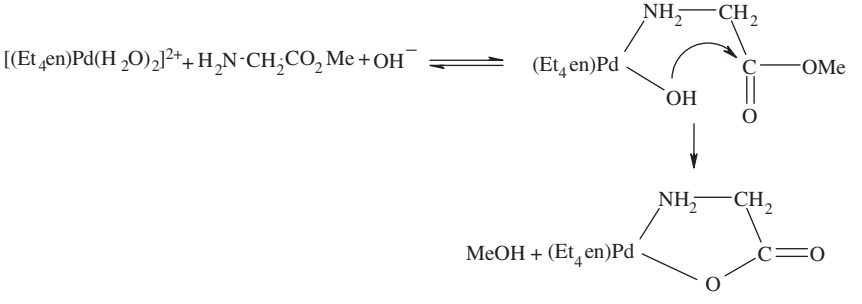
$$[Pd(Et_4en)L]^{2+} + OH^- \xrightarrow{k_{OH}} [Pd(Et_4en)L']^{+} + R'OH \tag{3}$$

Under the conditions used here, $NH_3^+CH(R)CO_2R'$ is bidentate giving $[Pd(Et_4en)(NH_2CH(R)CO_2R')]^{2+}$. The first-order dependence on OH^- concentration for this step may be accounted for by two mechanisms. One involves an initial rapidly established equilibrium in which the amino acid ester coordinates to palladium, followed by rate-determining OH^- attack (reaction (4), charges of complexes are omitted for simplicity).



(4)

The second involves rapid equilibrium formation of a Pd–OH complex, followed by intramolecular OH^- attack (reaction (5)).



(5)

In reactions of amino acid esters promoted by labile metal complexes, it has been difficult to establish whether one or a combination of the above mechanisms is involved in hydrolysis.

The kinetic data, volume of base added to keep the pH constant *versus* time, could be fitted by one exponential as shown in figure 1. Various other kinetic models were tested without leading to satisfactory fits of the data. Values of k_{obs} (the observed first-order rate constant at constant pH) were obtained (table 1). Plots of k_{obs} *versus* the hydroxide ion concentration were linear with a positive intercept (figure 2). The rate expression is therefore of the form equation (7).

$$\text{Rate} = k_{obs}[\text{Pd}(\text{Et}_4\text{en})(\text{ester})] \tag{6}$$

$$k_{obs} = k_o + k_{OH}[\text{OH}] \tag{7}$$

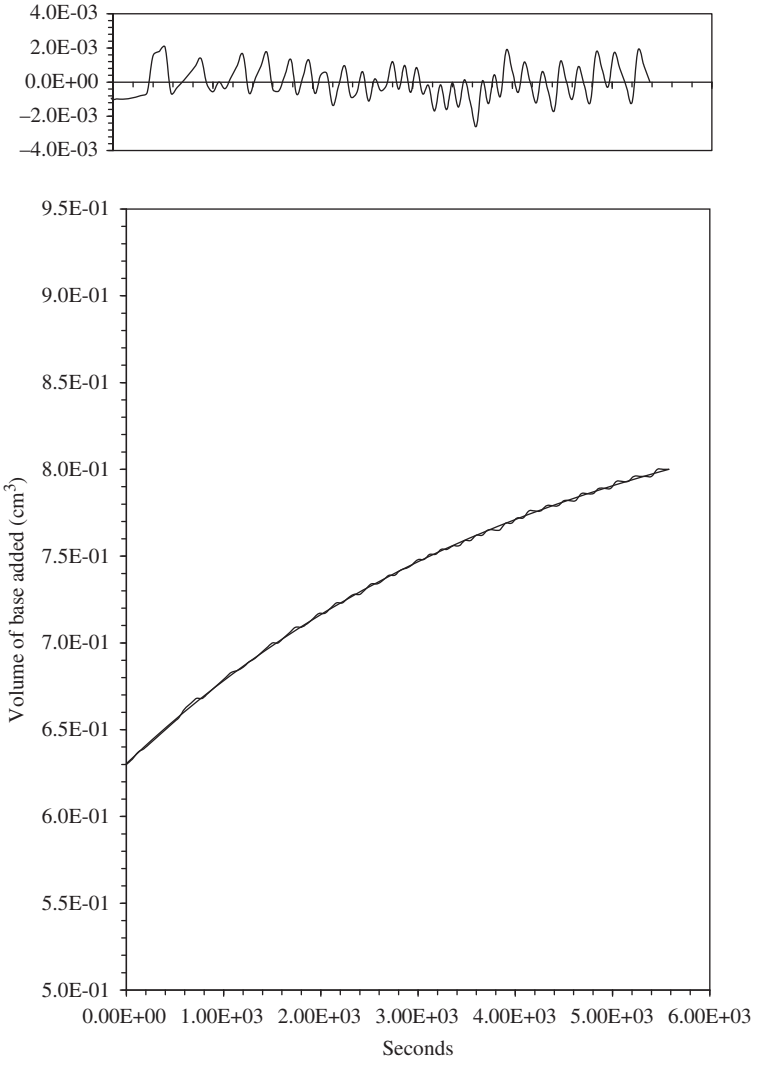


Figure 1. Typical values of the base-time trace for the hydrolysis of coordinated glycine methyl ester fitted with one exponential function. The top of the figure shows the value of base difference between measured and calculated kinetics traces.

The term k_o arises due to water attack on the mixed-ligand complex. Values of $k_{H_2O} = k_o/55.5$, where $55.5\,mol\,dm^{-3}$ is the molar concentration of water, were determined from the intercept and values of $k_{OH} = (k_{obs.} - k_o)/[OH]$ from the slopes of the plots. The various rate constants are given in tables 2 and 3.

The linear dependence of k_{obs} on $[OH^-]$ is consistent with direct attack of OH^- on the coordinated ester carbonyl group as given in reaction (4). Mechanism in reaction (5) requires that the plot of k_{obs} *versus* hydroxide ion concentration is not linear, while a plot of $1/k_{obs}$ *versus* $1/[OH^-]$ should be linear [13]. The rate acceleration denoted by the

Table 1. Kinetics of hydrolysis of coordinated amino acid ester in aqueous solution at 25°C.

System	pH	10^9 $[OH^-]$	$10^4 k_{obs}$ (s^{-1})
Glycine methyl ester	5.4	2.51	2.40
	5.6	3.98	2.90
	5.8	6.31	3.50
	6.0	10.00	4.57
	pH	10^5 $[OH^-]$	$10^4 k_{obs}$ (s^{-1})
Methionine methyl ester	9.0	1.00	1.40
	9.2	1.58	1.82
	9.4	2.51	2.40
	9.6	3.98	3.12
Histidine methyl ester	9.4	2.51	1.36
	9.6	3.98	1.73
	9.8	6.31	2.10
	10.0	10.00	2.85

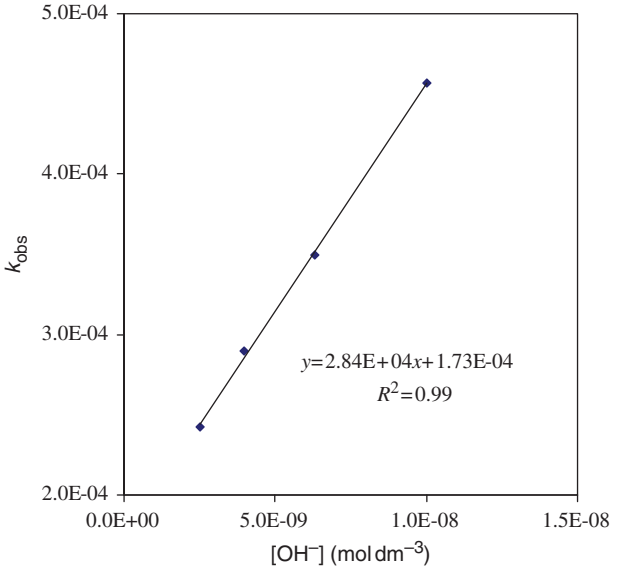


Figure 2. Plot of k_{obs} *vs.* $[OH^-]$ for hydrolysis of glycine methyl ester in water at 25°C.

Table 2. Rate constants ($k\,dm^3\,mol^{-1}\,s^{-1}$) for base hydrolysis of amino acid esters and their complexes at 25°C in aqueous solution.

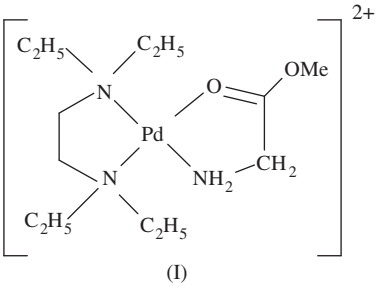
System	k_{OH}	$10^4\,k_o$	$k_{OH}^{ester\ a}$	C
Glycine methyl ester	2.88×10^4	1.70	1.28	2.25×10^4
Methionine methyl ester	5.72	0.74	0.77	7.43
Histidine methyl ester	1.95	0.32	0.62	3.15

[a]From Refs [4, 7].

Table 3. Rate constants ($k\,dm^3\,mol^{-1}\,s^{-1}$) for base hydrolysis of coordinated glycine methyl ester at different temperatures in aqueous solution.

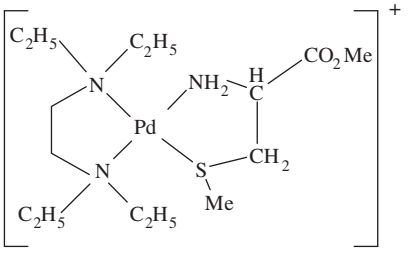
Temperature (°C)	k_{OH}	$10^4\,k_o$
15	2.36×10^4	1.58
20	2.65×10^4	1.68
25	2.84×10^4	1.73
30	3.13×10^4	1.43
35	3.44×10^4	1.33

catalysis ratio

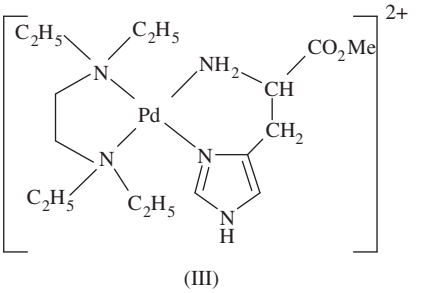


(I)

($C = k_{OH}/k_{OH}^{ester}$) is calculated (table 2) and found to be 2.25×10^4 for glycine methyl ester. Rate acceleration of this magnitude is fully consistent with the formation of a mixed-ligand complex where there is a direct interaction between Pd(II) and the carbonyl of the ester (structure I) as in reaction (4) [8, 10].



(II)



(III)

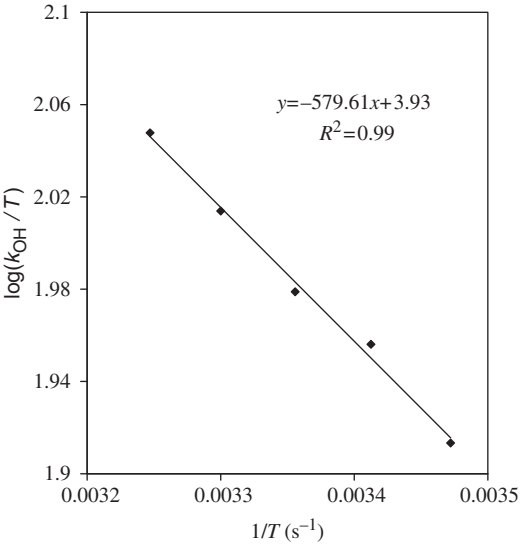


Figure 3. Plot of $\log(k_{OH}/T)$ *vs.* $1/T$ for hydrolysis of coordinated glycine methyl ester.

Formation of bidentate ester complexes with both copper(II) and cobalt(II) leads to rate accelerations [20, 21] of 10^5–10^6, and palladium(II) appears to be similar. Base hydrolyses of coordinated histidine and methionine esters were studied in the pH range 9–10. Throughout this pH range, the reactions show a first-order dependence on hydroxide concentration. The relative catalysis ratio observed with L-methylmethionate (L-MethOMe) [$k_{OH}/k_{OH}^{ester} = 7.43$] and methyl-L-histidinate (L-HisOMe) [$k_{OH}/k_{OH}^{ester} = 3.15$], table 2, suggests that in these cases the alkoxycarbonyl group is not bonded to palladium.

L-MethOMe complex is expected to have structure (II), in which the donors are thiolato-sulphur and α-amino. A similar situation (III) is likely with L-hisOMe, where the α-amino group and the pyridine nitrogen of the imidazole ring are donors. Previous studies have shown that formation of such complexes with non-bonded or pendant ester groups leads to only relatively small rate increases [20].

Comparative values of k_{OH} at 25°C for base hydrolysis of the glycine methyl ester incorporated in $[Pd(en)L]^{2+}$ is $4.88 \times 10^4\,dm^3\,mol^{-1}\,s^{-1}$ [21]. The k_{OH} for $[Pd(Et_4en)L]^{2+}$ (2.88×10^4) is lower than that of $[Pd(en)L]^{2+}$, indicating that steric interaction between the coordinated ester and the ethyl substituents attached to the amine lower the stability of the formed complex and consequently the rate of hydrolysis is lowered. This indicates that "fine tuning" of these metal centers using different inert ligands is thus possible.

The activation parameters for the hydrolysis of coordinated ester were determined using the Eyring equation of the form:

$$\log k_{OH}/T = -H^{\#}/2.303RT + \Delta S^{\pm}/2.303R$$

Plot of $(\log k_{OH}/T)$ *versus* $1/T$ (figure 3) has slope $-\Delta H^{\#}/2.303R$, from which the value of $\Delta H^{\#}$ is $11.10\,kJ\,mol^{-1}$ and the intercept is $\Delta S^{\pm}/2.303R$, from which $\Delta S^{\pm} = -122\,JK^{-1}\,mol^{-1}$ [22]. For base hydrolysis of free glycine methyl ester, the activation

Table 4. Rate constants (k $dm^3 mol^{-1} s^{-1}$) for base hydrolysis of coordinated glycine methyl ester in dioxane–water solution of different compositions at 25°C.

Dioxane (% v/v)	k_{OH}	$10^4 k_o$
12.5	0.57×10^5	2.49
25.0	1.37×10^5	2.43
37.5	3.24×10^5	2.35
50.0	5.29×10^5	2.36
62.5	8.78×10^5	1.79

parameters were [7] $\Delta H^{\#} = 39.7\,kJ\,mol^{-1}$ and $\Delta S^{\#} = -117\,JK^{-1}\,mol^{-1}$. The enhanced rate for base hydrolysis of the ester incorporated in $[Pd(Et_4en)L]^{2+}$ is therefore due to a decreased $\Delta H^{\#}$.

Solutions in biochemical micro-environments such as active sites of enzymes and side chains in proteins have dielectric constant values of 30–50 [23–26]. The dielectric constants of water and dioxane are 78.5 and 2.2, respectively [27]. Therefore, solution mixtures of dioxane–water solutions of different proportions have dielectric constants similar to those in biochemical microenvironment. Consequently, investigation of amino acid ester hydrolysis in dioxane–water mixtures is of biological significance. The rate constant for hydrolysis of coordinated glycine methyl ester was determined in various dioxane–water solutions of different composition. The hydrolysis rate constant k_{OH} (table 4) increases with increasing amount of dioxane. This may be accounted for on the basis that as the dioxane content increases the dielectric constant of the reaction medium decreases, favoring interaction of negatively charged OH^- with the electro-positive carbonyl carbon of the ester. Consequently, the hydrolysis process will be accelerated.

4. Conclusion

The hydrolysis of glycine methyl ester is catalyzed by $[Pd(Et_4en)(H_2O)_2]^{2+}$ with catalysis ratio, $C = 2.25 \times 10^4$. The catalytic effect is due to direct interaction between Pd(II) and the alkoxycarbonyl group of the ester species. However, hydrolyses of histidine and methionine methyl esters are not significantly catalyzed; the relative small catalysis-ratio values for the histidine and methionine methyl esters suggest that in these cases the alkoxycarbonyl group is not bonded to the metal ion. The solvent effect on the hydrolysis of ester shows that as the dielectric constant of the medium decreases (increasing dioxane content) hydrolysis of the ester is favored. This is interesting from the biological point of view since the solutions in biochemical micro-environment have dielectric constant values of 30–50, and the dielectric constant of water is 76.

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