

aqueous HCl solution. The reaction product was extracted three times with ether (20 ml  $\times$  3) and the organics were separated and dried over anhydrous magnesium sulfate. The ether was removed by rotatory evaporator. The GLC analysis indicated an exo/endo ratio of 83:17 (quantitative yield).

General procedure for endo-5,7-dimethyl-6,8-dioxabicyclo[3.2.1]octane (5). To a dried  $\text{ZnCl}_2$  (2 eq.) was added dropwise 0.2 g (1.4 mmol) of methyl vinyl ketone dimer (1) in 2 ml of  $\text{CH}_2\text{Cl}_2$  and 3 eq. of  $\text{Zn}(\text{BH}_4)_2$  (0.8M solution in THF) respectively at 0°C. After 2 hrs stirring at 0°C, 10 ml of 15% aqueous HCl solution was added to this reaction mixture and worked-up as above. The GLC analysis indicated an exo/endo ratio of 19:81 (quantitative yield).

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) of (4):  $\delta$  (ppm) 4.20 (1H, m), 3.99 (1H, br s), 1.70 (6H, br s), 1.42 (3H, s), 1.19 (3H, d,  $J = 10$  Hz).

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) of (5):  $\delta$  (ppm) 4.18 (2H, m), 1.70 (6H, br s), 1.42 (3H, s), 1.31 (3H, partially buried doublet).

IR (neat) of (4): 2935, 1460, 1443, 1380, 1237, 1185, 1099, 1011, 976, 839  $\text{cm}^{-1}$ .

IR (neat) of (5): 2934, 1464, 1442, 1379, 1259, 1190, 1097, 1020, 837  $\text{cm}^{-1}$ .

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## Initial State and Transition State Solvation for the Solvolysis of $\text{trans-[Co(N-eten)}_2\text{Cl}_2\text{]}^+$ in Binary Aqueous Mixtures: Excess Free Energy, Free Energy Cycle and Reaction Mechanism

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The rates of solvolysis of  $\text{trans-[Co(N-eten)}_2\text{Cl}_2\text{]}^+$  (N-eten; N-ethylethylenediamine) have been investigated using spectrophotometric method in binary aqueous mixtures containing methyl alcohol, isopropyl alcohol, *t*-butyl alcohol, ethylene glycol and glycerol. The values of  $\Delta H^\ddagger$  and  $\Delta S^\ddagger$  obtained from temperature effect on the rate constants were 80~84  $\text{kJ mol}^{-1}$  and -28~-45  $\text{JK}^{-1}\text{mol}^{-1}$ . Extrema found in the variation of the enthalpy and entropy of activation with solvent composition correlated very well with extrema in the variation of the physical properties of mixture which relate to sharp change in the solvent structure. The reaction mechanism was discussed in terms of correlation diagrams involving the excess molar Gibbs function of mixing for the binary mixtures. The behavior of this cobalt(III) complex was compared with that of *t*-butyl chloride. The application of free energy cycle to the process initial state to transition state in water and in the mixture showed that the solvation of transition state had dominant effect on the rates in the mixtures. It was found that  $S_N1$  character was increased with increasing the content of co-solvent in the mixture.

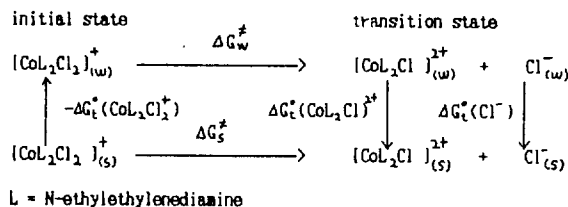
## Introduction

There have been numerous studies of solvolysis of cobalt

(III)-ammine complexes in mixed solvents.<sup>1-10</sup> The solvent effects on initial state and transition state in organic and inorganic reactions were published and reviewed.<sup>11-16</sup> It has

long been recognized that solvolysis reactions of the cobalt (III) complex have bond breaking dissociation mechanism involving the rate determining loss of a leaving group.<sup>17-21</sup>

Recently, free energy cycle<sup>5-10</sup> and excess free energy ( $G^E$ )<sup>22,23</sup> have been used in the diagnosis of reaction mechanism. The followings are application of free energy cycle relating the process initial state to transition state for the  $trans-[Co(N-eten)_2Cl_2]^+$  to give  $trans-[Co(N-eten)_2Cl]^{2+}$  together with the chloride in the transition state in water(w) and in the mixed solvent(s).



Equation (1) results from this cycle, where  $\Delta G_i^\circ(i)$  is the free energy of transfer for species  $i$  between water and the mixture.

$$\Delta G_s^\ddagger = \Delta G_w^\ddagger + \Delta G_i^\circ(CoL_2Cl^{2+}) + \Delta G_i^\circ(Cl^-) - \Delta G_i^\circ(CoL_2Cl_2^+) \quad (1)$$

Converting of free energies of activation,  $\Delta G^\ddagger$ , into first order rate constants, equation (1) can be rearranged to equation (2)

$$2,303RT \log(kw/ks) - \Delta G_i^\circ(Cl^-) = \Delta G_i^\circ(CoL_2Cl^{2+}) - \Delta G_i^\circ(CoL_2Cl_2^+) \quad (2)$$

Values for  $k$  can be determined experimentally and values for  $\Delta G_i^\circ(Cl^-)$  are available<sup>24</sup> for mixture of water with a range of co-solvents enabling the left hand side of equation (2) to be calculated. Therefore a positive value of left-hand side of equation (2) means that the effect of solvent structure on the ion in the initial state dominates over that on the ion in the transition state and negative value indicates the opposite.<sup>25</sup>

We here report the results of kinetic investigation of the solvolysis of  $trans-[Co(N-eten)_2Cl_2]^+$  in binary aqueous mixtures. The mechanism of solvolysis is represented by application of free energy cycle. It is investigated whether there is a correlation between the activation quantity ( $\Delta G^\ddagger$ ) calculated from the observed rate constant using transition state theory and the thermodynamic excess Gibbs function ( $G^E$ ) for binary aqueous mixture.

## Experimental

The complex  $trans-[Co(N-eten)_2Cl_2]Cl$  was prepared by using previously described method and the spectral data were consistent with literature values.<sup>26</sup> The reagents such as cobalt chloride, N-ethylethylenediamine and all organic solvents were of analytical grade. Mixed solvents were made up by weight percentages of which composition refer to weight percentages before mixing. The co-solvent for the mixtures were methyl alcohol, isopropyl alcohol, *t*-butyl alcohol, ethylene glycol and glycerol. Solvolysis reactions were followed spectrophotometrically at 532 nm by means of a Shimadzu-digital UV 210 spectrophotometer. The tem-

**Table 1.** Rate Constants and Activation Parameters for Solvolysis of  $trans-[Co(N-eten)_2Cl_2]^+$  in Water-Isopropyl Alcohol

| <i>i</i> -PrOH<br>w/w % | 25 °C | $k \times 10^4, \text{sec}^{-1}$ |      |       | $\Delta H^\ddagger$<br>kJmol <sup>-1</sup> | $\Delta S^\ddagger$<br>JK <sup>-1</sup> mol <sup>-1</sup> |
|-------------------------|-------|----------------------------------|------|-------|--------------------------------------------|-----------------------------------------------------------|
| 0                       | 2.65  | 4.32                             | 7.45 | 14.31 | 84                                         | -28                                                       |
| 5                       | 2.37  | 3.90                             | 6.84 | 12.55 | 84                                         | -32                                                       |
| 8                       | 2.31  | 3.50                             | 6.01 | 11.04 | 83                                         | -38                                                       |
| 10                      | 3.04  | 3.31                             | 5.70 | 10.12 | 80                                         | -46                                                       |
| 20                      | 1.99  | 3.15                             | 5.69 | 10.10 | 82                                         | -40                                                       |
| 25                      | 1.98  | 3.09                             | 5.39 | 9.82  | 81                                         | -44                                                       |
| 30                      | 1.95  | 3.07                             | 5.21 | 9.64  | 80                                         | -45                                                       |
| 44                      | 1.65  | 2.92                             | 5.09 | 8.52  | 82                                         | -41                                                       |

**Table 2.** Rate Constants for Solvolysis of  $trans-[Co(N-eten)_2Cl_2]^+$  in Binary Mixtures at 25 °C

| MeOH<br>w/w% | rates<br>$k \times 10^4$ | <i>t</i> -BuOH <sup>a</sup><br>w/w% | rates<br>$k \times 10^4$ | Glycol<br>w/w% | rates<br>$k \times 10^4$ | Glycerol<br>w/w% | rates<br>$k \times 10^4$ |
|--------------|--------------------------|-------------------------------------|--------------------------|----------------|--------------------------|------------------|--------------------------|
| 10.0         | 2.42                     | 5.0                                 | 2.55                     | 7.5            | 2.63                     | 4.9              | 2.61                     |
| 16.0         | 2.14                     | 10.0                                | 2.50                     | 10.0           | 2.60                     | 8.2              | 2.57                     |
| 20.0         | 2.01                     | 15.0                                | 2.50                     | 14.5           | 2.47                     | 10.0             | 2.54                     |
| 22.2         | 1.62                     | 20.0                                | 2.45                     | 19.3           | 2.43                     | 16.2             | 2.50                     |
| 28.4         | 1.56                     | 25.0                                | 2.31                     | 26.6           | 2.32                     | 20.0             | 2.36                     |
| 34.7         | 1.49                     | 30.0                                | 2.10                     | 30.0           | 1.94                     | 24.0             | 2.10                     |
| 40.0         | 1.38                     | 35.0                                | 1.94                     | 35.8           | 1.92                     | 30.0             | 2.07                     |
| 50.0         | 1.28                     | 40.0                                | 1.38                     | 49.3           | 1.72                     | 40.0             | 2.06                     |

<sup>a</sup> Rates constant and activation parameter were listed in ref. 28.

perature was maintained by Haake F 4391 circulator.

All kinetic experiments were performed in the presence of 0.01 M aqueous hydrochloric acid (pH 2), 0.5 M of ionic strength (adjusted with NaCl) and binary aqueous mixtures. In this acidic condition the side reaction to form hydroxo complex,  $trans-[Co(N-eten)_2OHCl]^+$  was repressed and negligible.<sup>27</sup> Rate constants were calculated from gradient of plots of  $\log(A_0 - A_\infty)/(A_t - A_\infty)$  against time  $t$  and at equilibrium, where  $A_0$ ,  $A_t$  and  $A_\infty$  indicate the absorbance of complex at time,  $t = 0$ ,  $t = t$  and  $t = \infty$ , respectively. Activation enthalpy ( $\Delta H^\ddagger$ ) and entropy ( $\Delta S^\ddagger$ ) were calculated by least square analysis of  $(\ln k_{obs}/T)$  against  $1/T$  in the usual way.

## Results and Discussion

The rate constants of solvolysis of  $trans-[Co(N-eten)_2Cl_2]^+$  in water and isopropyl alcohol mixtures were given in Table 1. Also the activation enthalpies and entropies were calculated and included. To investigate the solvent structure effect on the solvolysis, the rate constants with the solvent composition were given in Table 2. It was found that in every case an increase in solvent composition was accompanied by a decrease in the rates of solvolysis.

The analysis of solvent effects on rates of reaction is conveniently made using the formalism of transition state theory where by the rate constant for a particular reaction in a given solvent at fixed temperature and pressure is related to the activation Gibbs function,  $\Delta G^\ddagger$ .<sup>16</sup> In Table 1 and 2, the rate constants of solvolysis of  $trans-[Co(N-eten)_2Cl_2]^+$  in binary

aqueous mixtures were decreased in increasing of the co-solvent content. In this case, the reference solvent is pure water and new solvent is water + co-solvent mixture. Water is reactant to give product,  $\text{trans}[\text{Co}(\text{N-eten})_2\text{H}_2\text{OCl}]^{2+}$ . Thus this solvolysis in reference solvent is destabilized by water. However in the new solvent which contains less water, the reaction is more stabilized than reference solvent. Therefore  $\Delta G_s^*$  in new solvent is more positive than  $\Delta G_w^*$  in reference solvent.  $\Delta G^*$  increase as a result of differing effects of solvent on initial and transition states. This analysis is a pre-requisite to an analysis of the role of solvent structure in kinetic reaction. It also follows that measurements of  $\Delta G^*$  as a function of solvent can not yield detailed information concerning the underlying trends in initial and transition states stabilities. However it is clear that an understanding of the factors which control the dependence of kinetic parameters on solvent requires an identification of the direction and magnitude of the changes in the properties of initial and transition states.

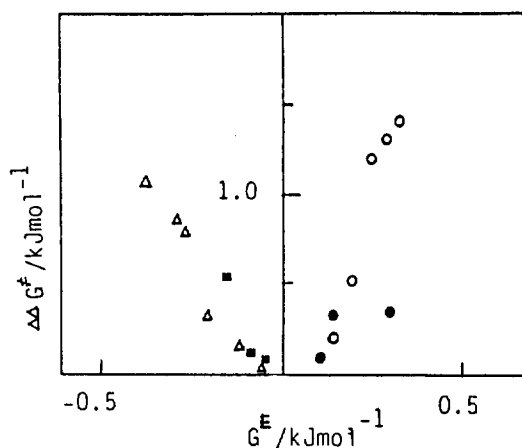
**Variation of Transition State Parameters with Solvent Composition.** As previously we reported,<sup>28,29</sup> a plot of  $\Delta H^*$  against  $\Delta S^*$  is linear despite irregular variation of  $\Delta H^*$  and  $\Delta S^*$  with solvent composition.  $\Delta H^*$  and  $\Delta S^*$  both showed minima in the region of mole fraction of *t*-butyl alcohol  $x_2 = 0.04$  and  $x_2 = 0.1$ . The similar trend was also shown in the isopropyl alcohol-water mixtures. These variation observed in Table 1, roughly correlated with the physical properties of solvent structure. The partial molar volume ( $V_2 - V_2^0$ ) of *t*-butyl alcohol and iso-propyl alcohol has a deep minimum at  $X_2 = 0.025$ <sup>30</sup> and  $X_2 = 0.04$ <sup>10,36,31</sup> respectively, and the excess enthalpy of mixing  $H^E$  has a minimum at  $x_2 = 0.25$ <sup>30</sup> and  $x_2 = 0.1$ .<sup>8,9,31-34</sup> These variations have also been reported for the solvolysis of *cis* and *trans*- $[\text{Co}(\text{en})_2\text{Cl}_2]^+$  in water-*t*-butyl alcohol mixtures.<sup>30</sup>

These extrema in physical properties at lower  $x_2$  in water and co-solvent mixtures are associated with sharp changes in solvent structure and show clearly the specific influence which solvent structure has on the transition state parameters. These variation can be explained as two aspects: the exertion of maximum strain by the branched chain alkyl group lying in the cavities between the 'flickering clusters' of structured water and the beginning of break down of the structure of the 'clusters' due to increasing stress within them.<sup>24</sup>

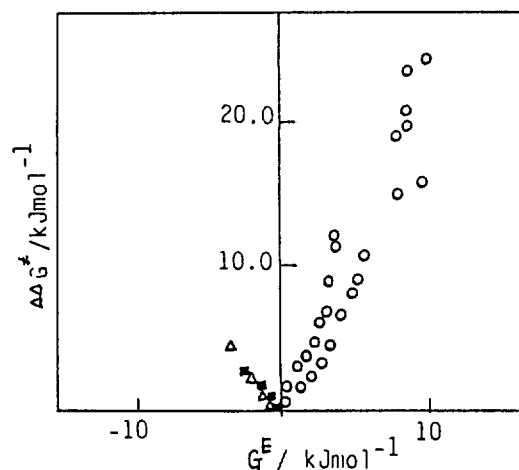
#### Excess Free Energy and Activation Free Energy.

There are interested in examining whether reactivities in substitution reactions in binary aqueous mixtures can be correlated with excess Gibbs free energies of mixing ( $G^E$ ) of the respective mixtures.  $G^E$  expresses the extend to the molar Gibbs function of mixing at given temperature, pressure, and mole fraction differs from that of the corresponding ideal liquid mixture.<sup>22,35</sup> Binary aqueous mixtures can be classified in three groups according to their excess molar thermodynamic functions of mixing. These are the 'typically aqueous (t.a.) mixtures' where  $G^E$  is positive and is dominated by its entropy component over the enthalpy component ( $|T\Delta S^E| > |H^E|$ ), 'typically non-aqueous positive (t.n.a.p.) mixtures' with positive  $G^E$  and  $|H^E| > |T\Delta S^E|$ , and 'typically non-aqueous negative (t.n.a.n.) mixtures' with negative  $G^E$  but again  $|H^E| > |T\Delta S^E|$ .<sup>36</sup>

Satisfactory results for solvolysis of the *trans*- $[\text{Co}(\text{N-eten})_2\text{Cl}_2]^+$



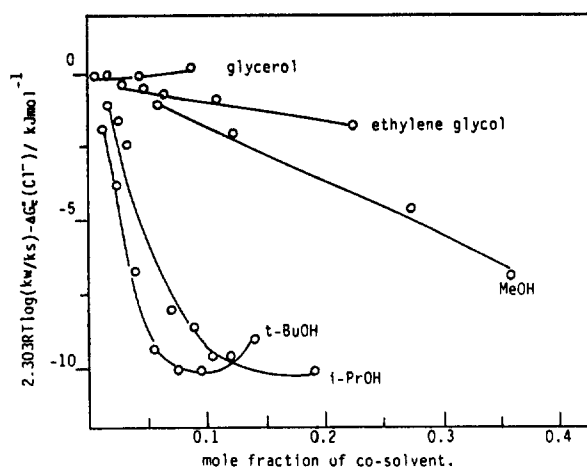
**Figure 1.** Relation between  $\Delta\Delta G^*$  and  $G^E$  for solvolysis of *trans*- $[\text{Co}(\text{N-eten})_2\text{Cl}_2]^+$  in binary mixtures. t.a. mixtures (○; MeOH, ●; *t*-BuOH). t.n.a. mixtures (Δ; glycol, ■; glycerol).



**Figure 2.** Relation between  $\Delta\Delta G^*$  and  $G^E$  for solvolysis of *t*-butyl chloride in binary mixtures. t.a. mixtures (○), t.n.a. mixtures (Δ; glycol, ■; glycerol).

$\text{eten})_2\text{Cl}_2]^+$  complexes have been obtained a range of t.a. mixtures containing alcohol and t.n.a.n. mixtures containing glycol or glycerol. In Figure 1, our kinetic results, in terms of the change in the Gibbs free energy of activation ( $\Delta\Delta G^*$ ), derived from transition state theory treatment of experimental rate constants were plotted against the respective  $G^E$  values.  $\Delta\Delta G^*$  represents the change in  $\Delta G^*$  on going from a solution in water(w) to a mixture(s) (i.e.,  $\Delta\Delta G^* = \Delta G_s^* - \Delta G_w^*$ ).<sup>22,23,36</sup>  $G^E$  values are obtained from published thermodynamic data. In Figure 2, there was a marked correlation between  $\Delta\Delta G^*$  and  $G^E$  for this reaction in such solvent mixtures. In view of the similarity of mechanism between the solvolysis of this cobalt(III) complex and solvolysis of *t*-butyl chloride, it is interesting to compare Figure 1 with an analogous plot, Figure 2 for the latter reaction. There were similar features common to Figure 1 and 2. It is clear that the mechanism of solvolysis of *trans*- $[\text{Co}(\text{N-eten})_2\text{Cl}_2]^+$  is similar to that of *t*-butyl chloride and there is satisfactory correlation between the kinetic and thermodynamic parameters.

**Application of Free Energy Cycle.** The free energy cycle discussed above could be applied to the rate constant of the solvolysis of this complex at 25°C. Here we should re-



**Figure 3.** Plot of  $2.303RT \log(kw/ks) - \Delta G^\ddagger(Cl^-)$  against mole fraction of co-solvent for solvolysis of  $trans-[Co(N-eten)_2Cl_2]^+$  in binary mixtures at 25 °C.

collect that the transfer free energy for  $i$  species,  $\Delta G^\ddagger_i$  means the differences between  $\Delta G^E(o)$  and  $\Delta G^E(i)$ , the excess free energies of mixing of the solvent with and without  $i$ .<sup>24</sup> The left hand side of eq.(2) plotted against mole fraction of co-solvent in Figure 3 showed negative values at all binary aqueous mixtures and all compositions. This means that  $|\Delta G^\ddagger(Co(N-eten)_2Cl_2^+)| > |\Delta G^\ddagger_i(Co(N-eten)_2Cl_2^+)|^{6-10}$ , i.e., the influence of solvent structure on the complex cation in the transition state is greater than that in the initial state. The more negative values of  $2.303RT \log(kw/ks) - \Delta G^\ddagger_i(Cl^-)$ , the more extension of the Co-Cl bond in the transition state. In other words,  $S_N1$  character is increased with increasing the negative value of eq. (2). In Figure 3, t.a. mixtures containing water + MeOH, water +  $i$ -PrOH and water +  $t$ -BuOH showed sharp change and more negative values but t.n.a.n mixtures such as water + glycerol and water + ethylene glycol have less negative values. The values of  $2.303RT \log(kw/ks) - \Delta G^\ddagger_i(Cl^-)$  were increased with increasing the content of co-solvent and increasing alkyl branch in water + alcohol mixtures.

These are due to the inducing effect of alkyl group, the solvation power of oxygen in  $t$ -butyl alcohol is stronger than that of in water for cation solvation. However, the value of left hand side of eq. (2) are increased to positive direction at  $x_2 = 0.09$  ( $t$ -butyl alcohol mixture) and  $x_2 = 0.15$  (isopropyl alcohol mixture). These are correspond to the co-solvent composition where the bulky alkyl chain of the co-solvent induce maximum structure formation within the surrounding flickering 'isoberg' of structured water and begining of the breakdown of the structure of the 'cluster' due to the increasing stress within them.<sup>30-34</sup> But these minima values are not observed in t.n.a.n mixtures which have not bulky alkyl chain.

It was found that the  $S_N1$  character of solvolysis of  $trans-[Co(N-eten)_2Cl_2]^+$  in binary aqueous mixtures are increased with increasing the co-solvent content and increasing size of alkyl chain in co-solvent.

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## Computer Graphics / Molecular Mechanics Studies of Quinolones Geometry Comparison with X-ray Crystal Structures

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Geometries for several representative quinolone carboxylate type antibacterials have been calculated by computer graphics/molecular mechanics energy minimization procedures using both MM2 and AMBER force fields. The calculated geometries were found to be in reasonable agreements with the corresponding X-ray crystal structures. It has been pointed out that notwithstanding the weaknesses associated with calculating the resonance and hydrogen bonding contributions, the employed methods are capable of generating credible ring geometries and torsional angle dispositions of N(1)-ethyl and 3-carboxylate substituents of the quinolones.

### Introduction

During the last decade or so, the 4-pyridone-3-carboxylate class of antibacterials, collectively known as quinolones, has been extensively explored in the pharmaceutical laboratories. Nalidixic acid, discovered more than 25 years ago as the first therapeutically useful quinolone, suffered from the lack of a substantial gram positive activity and the poor tissue distribution. In the early 1980's, significant improvements in potency and biospectrum were achieved with syntheses of 6-fluoro and 7-aminosubstituted derivatives, resulting in the development of currently marketed drugs such as norfloxacin, ciprofloxacin, pefloxacin, ofloxacin and enoxacin.<sup>1</sup>

Despite the clinical importance, the bacteriocidal mode of action of these compounds is not well understood. It is generally accepted that quinolones inhibit DNA-synthesis by interfering with the ATP-dependent DNA-supercoiling process catalyzed by bacterial DNA-gyrase. Fairly extensive studies have been carried out on the correlation between the minimum inhibitory concentration (MIC) and the *in vitro* gyrase inhibition, as well as on the binding of quinolones to DNA-gyrase and various natural and synthetic pieces of DNA in attempts to understand the molecular mechanism of the inhibition.<sup>2</sup> It was initially supposed that the mechanism of action might involve a covalent interaction between a bio-nucleophile on the A-subunit of the enzyme and the  $\beta$ -amino-enone moiety of quinolones, and that the nucleophilic 1,4-addition process might also be facilitated by a metal complexation with the  $\beta$ -keto-carboxylate moiety of the

quinolone structure.<sup>3</sup> However, the *in vitro* model experiments show that the quinolone ring system is not very susceptible to such a Michael attack by a number of organic nucleophiles.<sup>4</sup>

Very recently, Shen *et al.* have proposed a cooperative quinolone-DNA binding model for the inhibition of DNA-gyrase. According to this model, the initial binding of gyrase to the relaxed DNA substrate induces a specific quinolone binding site in the DNA in the presence of ATP. The binding affinity and specificity are derived from two key features, *i.e.*, the specific conformation of the proposed single-stranded DNA pocket induced by the enzyme and the unique self-association of the quinolone molecules to fit the binding pocket.<sup>5</sup>

In connection with our research program of using the computer-assisted molecular design (CAMD) technology to the mapping of receptor structures and to the design of suitable ligand molecules with pharmacological utility in the area of anti-infectives,<sup>6</sup> we have generated geometries of quinolone-type compounds by molecular mechanics calculations. We, herein, report the results of the calculated geometry, and compare them with the X-ray crystal structures in terms of accuracy and limitations.

### Results and Discussions

Selection of the quinolone structures for the molecular mechanics geometry calculation is primarily based on the limited number of quinolones and their analogs whose structures are accessible through the published literature or Cam-