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PREFACE.

The technique of ionizing a sample of molecules by gas-phase ion/molecule reactions was first reported in 1966 as an outgrowth of fundamental studies in gas-phase ion chemistry. In this pioneering paper, Munson and Field suggested that the method, which they called chemical ionization, might have useful analytical applications. The past 16 years have proven this prophecy to be abundantly correct. Chemical ionization provides information which is complementary to electron impact ionization in many cases and the two methods together are particularly powerful. As a result, chemical ionization is one of the most widely used ionization methods in mass spectrometry and it has found extensive application in structural elucidation studies and quantitative analytical studies in many branches of chemistry and biochemistry and in medical and environmental areas. At the same time chemical ionization studies have provided a large body of information concerning gas-phase ion chemistry.

The literature of chemical ionization mass spectrometry is now enormous and ranges from basic studies of the ionization processes to applied analytical problems where chemical ionization was the ionization method of choice. Numerous review articles have appeared covering various aspects of this literature, but these have necessarily been limited in scope. It appeared that there was a need for a more complete discussion of the field, particularly one which brought together the basic work which forms the body of knowledge upon which the applied studies are based. This is especially true because many people beginning work with chemical ionization mass spectrometry do not have a background in gas-phase ion chemistry. Accordingly, in the present book, I have chosen to emphasize such basic studies at the expense of the applied studies. In particular, the extensive fundamental studies of ion/molecule reaction kinetics and equilibria form the foundation upon which chemical ionization mass spectrometry is built and I have considered it desirable to review this work in some detail. At the same time I have not attempted to include the basic principles of mass spectrometry; these have received excellent coverage in other books.

The time necessary to write the manuscript was made available by a sabbatical leave for which I am indebted to the University of Toronto. The last half of the leave was spent at the École Polytechnique Fédérale, Lausanne, Switzerland, and I am indebted to the Institut de Chimie Physique and to Professor T. Gäumann for their kind hospitality. The excellent typing of Suzanne McClelland was invaluable as was the drafting work of Frank Safian. I am particularly indebted to the members of my research group and to my wife and family for their forbearance during my labors.

A.G.H.
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He received his Ph.D. in chemistry from McMaster University in 1956. After post-doctoral work at McMaster and the National Research Council of Canada, Ottawa, he joined the staff of the Department of Chemistry, University of Toronto, as a Lecturer in 1959, becoming Professor of Chemistry in 1967. In 1975, he spent six months as Visiting Professor in the Department of Molecular Sciences, University of Warwick and in 1982 he spent six months as Visiting Professor in the Institut de Chimie Physique, École Polytechnique Fédérale, Lausanne.

Dr. Harrison is a member of the Chemical Institute of Canada, the American Chemical Society, the Royal Society of Chemistry, and the American Society for Mass Spectrometry. He has served on the Board of Directors of the latter society and as chairman of the Physical Chemistry Division and Member of Council of the Chemical Institute of Canada. He is on the Editorial Advisory Boards of *Organic Mass Spectrometry* and *Mass Spectrometry Reviews*.

Dr. Harrison has authored or co-authored more than 150 papers in the area of mass spectrometry and gas-phase ion chemistry. His research interests lie in the chemistry of gas-phase ions and analytical applications of mass spectrometry.

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Chapter I

INTRODUCTION

I. PREFACE

The technique of chemical ionization (CI), first introduced by Munson and Field[1] in 1966, is a direct outgrowth of fundamental studies of ion/molecule interactions; as such the technique is based on the knowledge developed from these fundamental studies and makes use of the instrumentation developed for such studies. Since its initial introduction, chemical ionization mass spectrometry (CIMS) has developed into a powerful and versatile tool for the identification and quantitation of organic molecules and, consequently, has found extensive application in many branches of chemistry and biochemistry and in medical and environmental fields.

In CIMS ionization of the sample of interest is effected by gas-phase ion/molecule reactions rather than by electron impact, photon impact, or field ionization/desorption; frequently CIMS provides information which is complementary to these techniques rather than supplementary. Particularly in structure elucidation, it is common to determine both the electron impact (EI) and chemical ionization (CI) mass spectra. Although much of the earlier work in CIMS utilized positive ion/molecule reactions, there has been, in recent years, an increased interest in negative ion/molecule reactions as an ionization method. This later development of negative ion CIMS occurred, in part, because electron impact studies at low source pressures showed, in general, a low sensitivity for negative ion production as well as a strong dependence of negative ion mass spectra on electron beam energy. In addition, many commercial mass spectrometers were not equipped to operate in the negative ion mode. This latter problem has been largely rectified, while more recent studies have shown that negative ion signals under CI conditions are at least as strong and as reproducible as positive ion signals.

The essential reactions in chemical ionization are given in general form in Reactions 1 to 3. Ionization of the reagent gas (present in large excess), frequently by electron impact, usually is followed by ion/molecule reactions involving the primary ions and the reagent gas neutrals and produces the chemical ionization reagent ion or reagent ion array (Reaction 1).

$$e + R \xrightarrow{\quad R \quad} R^{+/-} \tag{1}$$

$$R^{+/-} + A \longrightarrow A_1^{+/-} + N_1 \tag{2}$$

$$A_1^{+/-} \longrightarrow A_2^{+/-} + N_2 \tag{3}$$

$$\longrightarrow A_3^{+/-} + N_3$$

$$\longrightarrow A_i^{+/-} + N_i$$

This reagent ion or reagent ion array represents the stable end product(s) of the ion/molecule reactions involving the reagent gas. Collision of the reagent ion(s), $R^{+/-}$, with the additive (present at low concentration levels, usually <1% of the reagent gas) produces an ion, $A_1^{+/-}$, characteristic of the additive (Reaction 2). This additive ion may fragment by one or more pathways, as in Reaction 3, or, infrequently, react with the reagent gas; the final array of ions $A_1^{+/-}$ to $A_i^{+/-}$, when mass analyzed in the usual manner, provides the chemical ionization mass spectrum of the additive A as effected by the reagent gas R.

A large part of the usefulness of CIMS rests with the fact that a large variety of reagent gases, and hence, reagent ions, can be employed to effect ionization. To a considerable extent the choice of reagent systems can be tailored to the problem to be solved. The problems amenable to solution by the chemical ionization technique can be divided into three rough categories: (1) molecular weight determination, (2) structure elucidation, and (3) identification and quantitation.

II. MOLECULAR WEIGHT DETERMINATION

When a gaseous sample of a polyatomic species is bombarded with electrons at sample pressures of $\sim 10^{-5}$ torr, the initial electron/molecule interaction produces an assembly of molecular ions with internal energies (relative to the ground state of the molecular ion) ranging from 0 to 10 eV. For some classes of compounds the critical internal energy required for fragmentation of the molecular ion is extremely low (or zero) with the result that no molecular ions are seen in the electron impact mass spectrum; in effect fragmentation is so facile that no molecular ions survive for the $\sim 10^{-5}$ sec that elapses before mass analysis occurs. When this happens the molecular weight of the sample molecules can be established only with considerable difficulty by electron impact methods. The aim of chemical ionization in these instances is to produce, by suitable choice of reagent ions, abundant ions characteristic of the sample and providing the molecular weight of the sample molecules.

In positive ion chemical ionization the most commonly used ionization reaction for such purposes has been proton transfer (Reaction 4) from the reagent ion(s), XH^+, to the sample molecule M, where ΔH_4 is given by the proton affinity (PA) of X less the PA of M.

$$XH^+ + M \rightarrow MH^+ + X, \; \Delta H_4 \tag{4}$$

The extent of fragmentation of MH^+ depends on its internal energy which, in turn, is dependent on the exothermicity of the proton transfer reaction. The magnitude of ΔH_4, and thus the extent of fragmentation of MH^+, usually can be controlled by suitable choice of reagent gas; in addition, the stability of the even-electron MH^+ ion may be considerably greater than the stability of the odd-electron $M^{+\cdot}$ species formed in the electron impact process.

An analogous proton transfer (Reaction 5) has been utilized in negative ion chemical ionization; ΔH_5 is equal to $PA([M-H]^-) - PA(X^-)$ or, alternatively

$$X^- + M \rightarrow [M-H]^- + HX \tag{5}$$

is given by the gas-phase acidity of M less the acidity of XH; again by suitable choice of reagent ion the exothermicity of the proton transfer reaction can be made sufficiently small as to preclude extensive fragmentation of $[M-H]^-$. In addition, the exothermicity of the reaction appears to reside primarily in the bond formed between X and H and therefore is unavailable to promote fragmentation of $[M-H]^-$.

A number of other reactions also have been used to provide molecular weight information. These include hydride abstraction (Reaction 6), electron attachment (Reaction 7), electron transfer (Reaction 8), and adduct or cluster ion formation (Reaction 9).

$$X^+ + M \rightarrow [M-H]^+ + XH \tag{6}$$

$$e + M \rightarrow M^{-} \tag{7}$$

$$X^{\ddot{\cdot}} + M \rightarrow M^{\ddot{\cdot}} + X \tag{8}$$

$$X^{+/-} + M \rightarrow M \cdot X^{+/-} \tag{9}$$

It should be noted that formation of cluster ions usually requires third-body collisional stabilization and the rates of such reactions are likely to be considerably slower than the rates of bimolecular processes such as Reactions 4 to 8.

In the early literature, ions characteristic of molecular weight frequently were called quasi-molecular ions independent of their exact nature as MH^+, $[M-H]^{+/-}$, or $M \cdot X^{+/-}$. Fortunately this terminology largely seems to have been discontinued; the characteristic ions from which the molecular weight is established should be clearly identified and not hidden under a generic name.

III. STRUCTURE ELUCIDATION

When a sample of unknown chemical structure is being examined one usually desires structural information, in addition to molecular weight information, from the chemical ionization mass spectrum. Ideally, one would like an array of reagent ions which give specific characteristic reactions with each possible functional group thus signaling the presence or absence of a particular group. Except for a very few cases this ideal has not been attained, and consequently other approaches must be used.

The majority of structural studies to date have used positive ion proton transfer chemical ionization methods. The major fragmentation reactions of the even-electron MH^+ ions formed in Reaction 4 involve elimination of stable neutral molecules, HY, where Y is a functional group such as OR, NR_2, halogen, etc., present in the molecule. This fragmentation mode frequently is quite different from the fragmentation modes of the odd-electron molecular ions formed by electron impact ionization, and the structural information obtained by the two techniques often is complementary. The extent of fragmentation of MH^+ depends not only on the exothermicity of the protonation reaction but also on the nature of the functional group Y and on the identity of the fragment ion formed. In most cases, by a suitable choice of proton transfer reagent ions, both molecular weight and structural information can be obtained.

In those cases where the fragment ions formed by EI are structurally illuminating but no molecular weight information is provided by the EI mass spectrum, mixed proton transfer/charge exchange reagent systems can be used. The proton transfer reagent forms MH^+ ions indicative of molecular weight, while the charge exchange reagent, by dissociative charge exchange, gives the same fragment ions as are produced in EI since the initial ion/molecule interaction produces the odd-electron molecular ion.

The methodology of structure elucidation by negative ion chemical ionization is much less developed and impossible to generalize in an introductory chapter.

IV. IDENTIFICATION AND QUANTITATION

This application of mass spectrometry is undoubtedly the most common, whether employing electron impact or chemical ionization. The aim is to identify a known substance and to measure quantitatively the amount of this substance present in a frequently complex matrix. In CIMS three basic approaches can be used for identification. In the first, the component of interest is selectively ionized by a suitable reagent without separation, or with minimal separation, of the mixture. It is essential that the other components either not be ionized or, alternatively, that they not produce ions which are isobaric with those from the component of interest. Because of these restrictions this simple approach has been employed relatively infrequently. However, it should gain in popularity as specific ionization reactions are developed.

In the vast majority of studies separation of the mixture is achieved by gas chromatography or liquid chromatography with direct introduction of the chromatographic effluent into the mass spectrometer ion source. The ionization reaction requires only that one or more ions characteristic of the component of interest be produced in high yield to achieve maximum sensitivity of detection; these ions may be MH^+, $[M-H]^+$, $[M-H]^-$, or fragment ions. In general, formation of two or more ions is preferred since identification is made more certain by the requirements that the appropriate ion signals must show the same intensity-time profile as well as the appropriate relative intensities.

An alternative to separation of the components by chromatographic methods is separation of the components by mass spectrometric methods: so-called MS/MS experiments. In this approach the complex mixture is ionized, usually by gentle methods, to produce characteristic ions such as MH^+ or $[M-H]^-$ from each component. The ion suspected to arise from the component of interest is selected by mass analysis in the first stage of the double mass spectrometer, and its identity confirmed by mass analysis in the second stage of the instrument from the fragment ions arising from collision-induced dissociation of the selected ion.

The problems of quantitation, particularly in gas chromatography/mass spectrometry work, have been discussed in detail.[2] Because of potential losses during the workup and chromatographic steps, an internal standard usually is added to the mixture at the earliest possible stage of sample handling. This internal standard should have chemical and physical properties similar to the component of interest so that the losses of the two will be the same. Knowing the amount of standard introduced the amount of unknown present can be deduced from a comparison of the response of the mass spectrometer to the unknown and the standard. Three types of internal standards have been employed, (a) a stable isotope-labeled analogue of the compound to be measured, (b) a homologous compound which yields a fairly intense ion in common with the compound to be measured, and (c) a compound which yields a different ion but which has similar chemical and physical properties. Obviously, the type (b) standard cannot be used in the absence of temporal separation of the components by chromatography, while both type (a) and type (c) standards can be used with both chromatographic and nonchromatographic sample introduction.

V. SCOPE OF THE PRESENT WORK

These introductory comments serve to indicate the scope of the present monograph. CIMS rests firmly on the foundations established from fundamental studies of gas-phase ion chemistry. These foundations are discussed in Chapter 2. The techniques of mass spectrometry peculiar to chemical ionization studies are discussed in Chapter 3, although no attempt is made to review the basic principles of mass spectrometry; for these the reader is referred to other sources.[3-6] The reagent gases used in CIMS have been many, with various areas of utility; the more important are discussed in Chapter 4. Similarly, the range of compounds studied by chemical ionization mass spectrometry is vast. Those for which systematic studies have been made, allowing generalizations to be drawn, are discussed in Chapter 5. Finally, a number of more specialized topics are discussed in Chapter 6.

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Chapter 2

FUNDAMENTALS OF GAS PHASE ION CHEMISTRY

I. INTRODUCTION

From the earliest days of mass spectrometry, ions were observed which generally were agreed to have arisen from reactions between ions and neutral molecules. An ion of $m/z = 3$ was observed by Dempster[1] in 1916 and identified as H_3^+; its formation by Reaction 1 was well established by 1925.[2,3]

$$H_2^{+\cdot} + H_2 \rightarrow H_3^+ + H^\cdot \tag{1}$$

In 1928 Hogness and Harkness[4] reported the formation of both I_3^+ and I_3^- in iodine vapor subjected to electron impact. Ion/molecule reactions were observed in several other systems during the 1920s; the early work has been reviewed by Smyth[5] and by Thompson.[6] With improvements in instrumentation and techniques, particularly vacuum technology, the nuisance of secondary processes was largely eliminated and studies of ion/molecule reactions largely ceased. The main interests in mass spectrometry during the period 1930 to 1950 lay in the physics of ionization and dissociation, in the precise determination of isotopic masses and abundances, and in the development of analytical mass spectrometry.

The modern era of ion/molecule reaction studies began in the early 1950s when the ion CH_5^+, formed by the reaction

$$CH_4^{+\cdot} + CH_4 \rightarrow CH_5^+ + CH_3^\cdot \tag{2}$$

was independently discovered by Tal'roze and Lyubimova[7] in the U.S.S.R. and by Stevenson and Schissler[8] and Field et al.[9] in the U.S. The observation of CH_5^+ as a stable species aroused the interest of chemists concerned with structure and bonding, while the observation that Equation 2 was considerably faster than reactions involving only neutral species suggested that ion/molecule reactions might play an important role in radiation chemistry and aroused the interest of the radiation chemists. In addition, much improved equipment was available for the controlled study of ionic collision processes. As a result a number of studies of gas-phase ion/molecule reactions were undertaken. Since that beginning the study of the products, distribution, rates, and equilibria of gas-phase ionic reactions has become a major field of scientific activity with applications in many diverse fields. In the course of these studies many advances in instrumentation have been made. The advances in instrumentation and in the understanding of gas phase ion chemistry have been reviewed in numerous articles[10-19] and books.[20-27]

The instrumentation developed for the study of ion/molecule reactions has led to the instrumentation for chemical ionization mass spectrometry; this aspect is discussed in Chapter 3. The large body of kinetic and thermochemical data derived from the fundamental studies constitutes the foundation upon which the chemistry of the chemical ionization technique is based; this body of data is reviewed in the remainder of this chapter.

II. ION/MOLECULE COLLISION RATES

The usefulness of an ion/molecule reaction in a chemical ionization system depends in part on the identity of the reaction products, and in part on the rate of the reaction.

The latter is important since only those reactions which are rapid can be expected to show adequate product ion yields. The upper limit to the reaction rate is given by the collision rate. The present section reviews the estimation from theory of collision rates of ions with nonpolar and with polar molecules.

A. Langevin Ion-Induced Dipole Theory

When an ion interacts with a nonpolar neutral molecule it induces a dipole in the neutral, the magnitude of which depends on the polarizability of the molecule; at moderately long range the only interaction of importance is the resultant ion-induced dipole interaction. Eyring et al.[28] first calculated in 1936 the classical capture collision cross section for the reaction $H_2^+ + H_2$ using absolute rate theory and a model of a structureless point charge interacting with a point-polarizable molecule. A general form of the capture collision cross section was derived by Vogt and Wannier,[29] and elaborated by Gioumousis and Stevenson[30] based on a model first developed by Langevin.[31] The theoretical development has been discussed extensively by a number of authors;[16,32-34] the present summary is based largely on the treatment of Su and Bowers.[34]

The theory calculates the collision cross section for an ion/molecule pair with a given relative velocity where both the partners are assumed to be point particles with no internal energy and the interaction between the two is assumed to arise from ion-induced dipole forces only. Thus for an ion and a molecule approaching each other with a relative velocity v and impact parameter b (Figure 1) the classical potential at an ion/molecule separation r is given by

$$V(r) = -\alpha q^2 / 2r^4 \tag{3}$$

where α is the polarizability of the neutral and q is the charge on the ion. For $r < \infty$ the relative energy of the system, E_r, is the sum of the instantaneous kinetic energy and the potential energy

$$E_r = \frac{1}{2} \mu v^2 = E_{kin}(r) + V(r) \tag{4}$$

where μ is the reduced mass. There are two components to $E_{kin}(r)$, the translational energy along the line of center of the collision, $E_{trans}(r)$, and the energy of relative rotation of the particles, $E_{rot}(r)$, where the latter is given by

$$E_{rot}(r) = L^2 / 2\mu r^2 = \mu v^2 b^2 / 2r^2 \tag{5}$$

where L is the classical orbital angular momentum of the two particles. The rotational energy is associated with an outwardly acting centrifugal force and the effective potential of the ion/molecule system can be represented as the sum of the central potential energy and this centrifugal potential energy

$$V_{eff}(r) = -(\alpha q^2 / 2r^4) + (L^2 / 2\mu r^2) \tag{6}$$

The total relative energy of the system thus is

$$E_r = E_{trans}(r) + V_{eff}(r) \tag{7}$$

The variation of $V_{eff}(r)$ with r at constant E_r depends on the value of the impact parameter b. For b = 0 there is no contribution from the centrifugal potential and $V_{eff}(r)$ is attractive for all values of r. When b > 0 the centrifugal potential term creates a so-called "centrifugal barrier" to a capture collision. The special case (b = b_c) where the centrifugal barrier height equals E_r is shown in Figure 2; at r_c $V_{eff}(r) = E_r$ and,
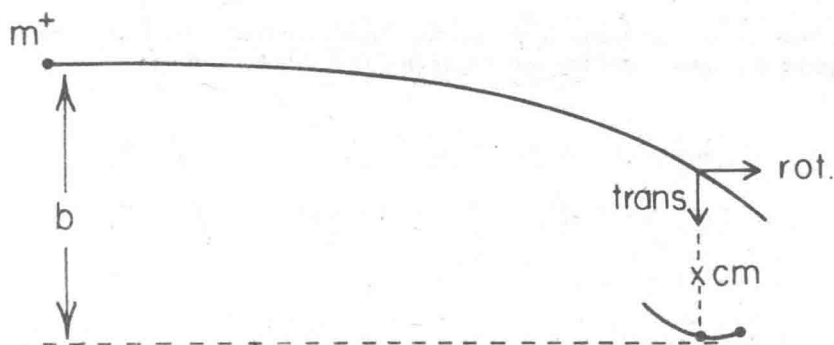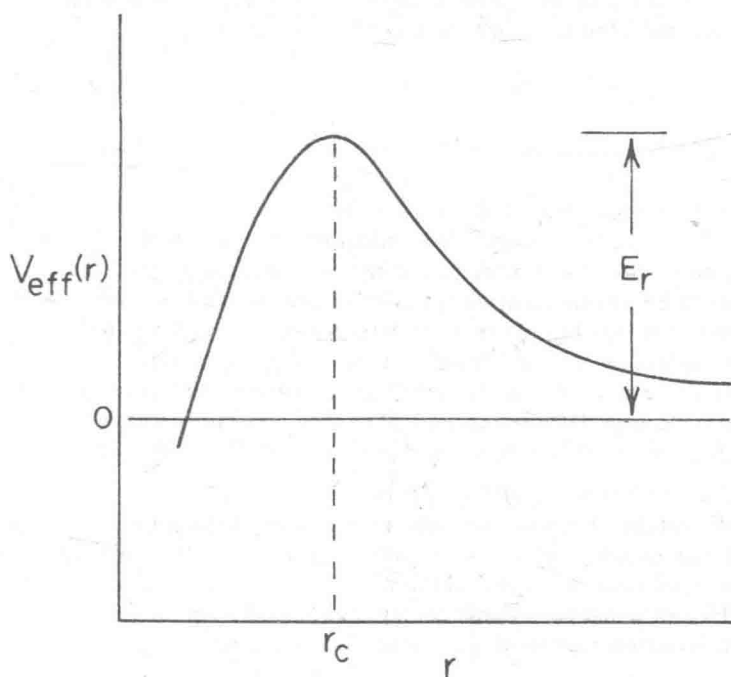
FIGURE 1. Schematic ion/molecule collision.

FIGURE 2. V_{eff} vs. r for critical impact parameter b_c.

thus, from Equation 7 $E_{trans}(r) = 0$ and the particles will orbit the scattering center with a constant ion/molecule separation r_c. For all impact parameters less than b_c a capture collision will occur where a capture collision is defined as one in which the particles have appropriate energy and impact parameters to pass through $r = 0$. (For real ions and molecules there would, of course, be some finite minimum value of $r > 0$.) For impact parameters greater than b_c the centrifugal barrier prevents capture and the particles are simply scattered at large values of r.

The capture collision cross section at a given velocity v is defined by

$$\sigma(v) = \pi b_c^2 \tag{8}$$

The critical impact parameter b_c is thus the impact parameter such that $V_{eff}(r) = E_r$ and can be evaluated from the conditions that $\partial V_{eff}(r)/\partial r = 0$ and $V_{eff}(r) = E_r$ at r $= r_c$, i.e.,

$$\partial V_{eff}/\partial r = 0 = (L^2/\mu r^3) + (2\alpha q^2/r^5) \tag{9}$$

$$V_{eff}(r) = (L^2/2\mu r^2) - (\alpha q^2/2r^4) = E_r = \frac{1}{2} \mu v^2 \tag{10}$$

These restrictions lead to

$$r_c = (2q/b_c v)(\alpha/\mu)^{1/2} \tag{11}$$

$$b_c = (4q^2\alpha/\mu v^2)^{1/4} \tag{12}$$

which lead to the distance of closest approach $r_c = b_c/2^{1/2}$ and to a capture collision cross section and collision rate constant given by

$$\sigma_c(v) = \pi b_c^2 = (2\pi q/v)(\alpha/\mu)^{1/2} \tag{13}$$

$$k_c = v \cdot \sigma_c(v) = 2\pi q(\alpha/\mu)^{1/2} \tag{14}$$

Hence, if only ion-induced dipole interactions are involved, classical collision theory predicts that the capture cross section should vary inversely as the relative velocity of the colliding pair while the capture rate constant, frequently called the Langevin rate constant, should be independent of the relative velocity and the temperature. As will be seen in the following, Equation 14 predicts reasonably well the maximum rate constants for ion/molecule reactions involving nonpolar molecules. This indicates that a reaction occurs on every collision for many ion/molecule pairs; consequently there can be no activation energy for the reaction. The rate constant predicted from Equation 14 is of the order of 1×10^{-9} cm³ molecule⁻¹ sec⁻¹ or 6×10^{11} l mol⁻¹ sec⁻¹.

B. Average Dipole Orientation (ADO) Theory

Although Equation 14 predicts reasonably well the maximum rate constants for reactions involving nonpolar molecules it underestimates the rate constants of most ion/molecule reactions involving polar molecules. For these cases it was shown first by Moran and Hamill[35] that ion-dipole forces could not be ignored. Where such forces are important the effective potential analogous to Equation 6 becomes

$$V_{eff}(r) = (L^2/2\mu r^2) - (\alpha q^2/2r^4) - (\mu_D q\cos\theta/r^2) \tag{15}$$

where μ_D is the dipole moment and θ is the angle the dipole makes with the center of collision. Hamill and colleagues[35,36] made the simplifying assumption that the dipole "locks in" on the ion ($\theta = 0$) and derived, by the approach outlined above, the capture collision rate constant

$$k_{LD}(v) = (2\pi q/\mu^{1/2})[\alpha^{1/2} + (\mu_D/v)] \tag{16}$$

where the subscript LD refers to the locked-in dipole approximation. In this case the rate constant depends on the relative velocity of the colliding pair and gives[37] for a thermal Maxwell-Boltzmann distribution of relative velocities

$$k_{LD}(therm) = (2\pi q/\mu^{1/2})[\alpha^{1/2} + \mu_D(2/\pi k_B T)^{1/2}] \tag{17}$$

where k_B is Boltzmann's constant and T is the absolute temperature.