Journal of Molecular Structure, 107 (1984) 139—155
THEOCHEM
Elsevier Science Publishers B.V., Amsterdam — Printed in The Netherlands

CLASSICAL DYNAMICS STOCHASTIC THEORIES OF CHEMICAL REACTIONS[+]

J.A.N.F. GOMES
Dep. de Quîmica, Faculdade de Ciências, 4000 PORTO(PORTUGAL)

ABSTRACT

Kramers theory of the rates of chemical reactions is reviewed and some recent advances are surveyed. A special attention is given to extensions of the theory to models with more than one coordinate It is stressed that important new features may arise from the coupling of the reaction coordinate to unreactive normal modes.

1. INTRODUCTION

Classical dynamics stochastic theories of chemical reactions have received a great deal of attention in recent years. The approach originally used by Kramers[1,2] has been generalized and new domains of application discussed. In this section I shall present the main ideas of Kramers' model and summarize its major results.

A multitude of processes in Physics and Chemistry involve the activated escape of a "particle" over a barrier: the dynamics of

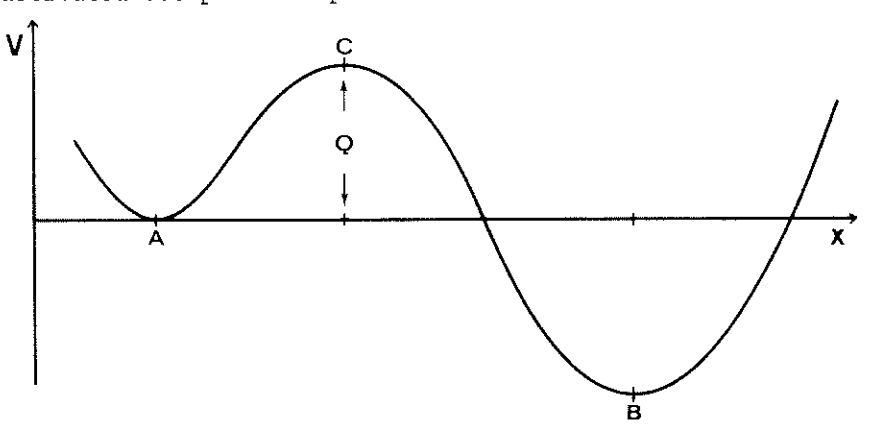

Fig. 1. One-dimensional double well potential.

(+) Presented at the XIVth Congress of the Quantum Chemists of Latin Expression, Louvain-la-Neuve (Belgium), 29.May-2.June, 1983.

0166-1280/84/$03.00

certain spin-glass models; the diffusion; the surface catalysis; the electron or proton transfer; the reactions in proteins; the chemical reactions in solution. The common feature of these models is that a particle is considered to be in a double well potential (Fig. 1). The two well regions, A and B, may be identified with "reactants" and "products" and are separated by a potential barrier in the region C. Furthermore, the particle is assumed to be under the effects of a "heat-bath" which acts through irregular forces that must be added to the systematic, deterministic force originating from the potential $V(x)$.

Kramers considered an ensemble of particles, initially all in well A, and studied their subsequent escape over the barrier, this process being identified with the chemical reaction. No back migrations across C into the left-hand side well are considered, what is better represented by the one-well potential in Fig. 2.

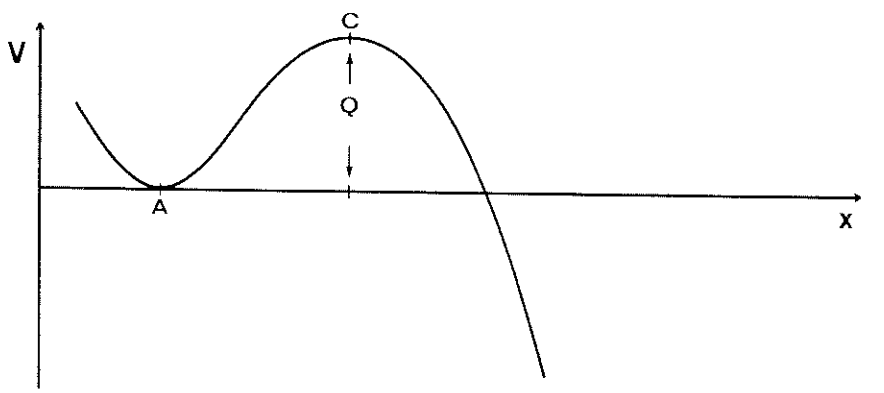

Fig. 2. Kramers potential model.

The probability distribution of the particles in phase space (position and velocity) is governed by an equation of motion of a general class known as Fokker-Planck equations. In order to obtain simple analytical results, Kramers made a number of simplifying hypotheses, namely (i) the potential is parabolic near A ($V(x) \simeq \simeq \frac{1}{2}\omega_A^2 x^2$) and near C ($V(x) \simeq Q - \frac{1}{2}\omega_C^2 x^2$) and (ii) the height of the barrier is much larger than the thermal energy, $Q >> \kappa T$, so that the escape of particles over the barrier is very slow and the

equilibrium distribution in the well is very little disturbed. Under this assumption, the following general expression for the rate escape was obtained[1,2]

$$K = \frac{\omega_A}{2\pi\omega_C}\left[(\beta^2/4 + \omega_C)^{1/2} - \beta/2\right] \exp(-Q/\kappa T) \qquad (1)$$

where β is proportional to the dynamical friction, η (see below). This expression contains the correct Arrhenius factor and the pre-exponential part depends on the shape of the potential and the viscosity of the medium. Two limit cases of eq. (1) may be of some interest.

(I) The overdamped case. When the friction is very high, $\beta >> 2\omega_C$, the heat bath interacts rapidly with the ensemble of particles so that the thermal equilibrium of the velocity coordinate is maintained. In this situation eq. (1) may be simplified to

$$K = \frac{\omega_A\ \omega_C}{2\pi\ \beta} \exp\ (-Q/\kappa T),\ (\beta >> 2\omega_C). \qquad (2)$$

This very result may be obtained directly if, instead of the general Fokker-Planck equation for the distribution $W(x,u,t)$, one considers the so called Smoluchowski equation, the equation of motion of the probability distribution in position space, $W(x,t)$. This latter equation is obtained on the assumption that thermal equilibrium is always maintained in the velocity as we shall discuss below. The particles will then have a purely diffusional motion.

(II) The intermediate friction case. If we assume $\beta << 2\omega_C$ to be valid eq. (1) is simplified to

$$K = \frac{\omega_A}{2\pi} \exp\ (-Q/\kappa T),\quad (\beta << 2\omega_C). \qquad (3)$$

This is the same expression as obtained in transition state theory (TST). The coupling to the heat bath is sufficiently weak for the barrier crossing to be negligibly perturbed but it is sufficiently high to provide a continued equilibrium distribution of reactive high energy species.

(III) The very small friction case. When the reactive system interacts very weakly with the medium, eq. (1) fails as the reaction

rate is governed by the energy flow within the well up to the threshold value of the barrier height. Kramers[1] showed that, in this region the reaction rate increases with the increase of the viscosity of the medium. As shown by Grote and Hynes[3], for low barriers (relative to κT) the rate constant is reduced by the inefficient energy transfer in the bottom portion of the well; for large barriers, the much more efficient non-adiabatic regime near the top of the barrier may become dominant.

The three kinetic regimes just discussed may be represented schematically as in Fig. 3.

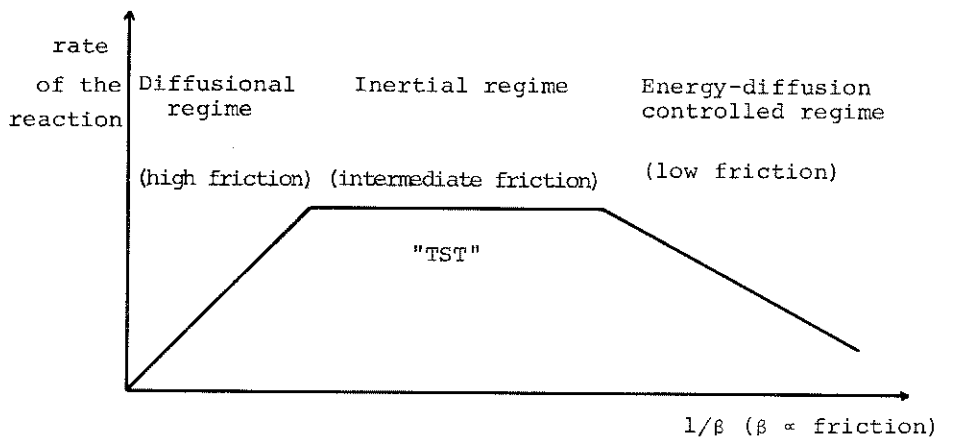

Fig. 3. Reaction rate regimes according to Kramers.

Before starting the discussion of more specific topics of reaction rate theory, it may be useful to outline some general results of the theory of Brownian motion[4] that is instrumental to Kramers theory and to the more advanced models discussed later in this paper. Consider a particle (assumed spherical for simplicity) of radius a and mass m that moves in an external field of force but, in addition to this, is subject to irregular forces from the surrounding medium which is assumed in thermal equilibrium. The equation of motion of the particle may be written in the form of a Langevin equation,

$$u = \dot{x}$$

$$\dot{u} = -\beta u + F(x,t) + A(t) \qquad (4)$$

where $(-\beta u)$ represents the dynamical friction with

$$\beta = 6\pi\, a\, \eta/m \tag{5}$$

and η is the coefficient of viscosity. $F(x,t)$ is a deterministic force which is related to some potential as

$$F = -\frac{dV}{dx} . \tag{6}$$

$A(t)$ is a fluctuating force which is assumed (i) independent of u and (ii) to vary very rapidly as compared to the variations of u. A solution of the stochastic differential equation (4) is to be understood as a probability distribuition $W(u,t;\, x_o,u_o)$ for the velocity of the particle given the initial velocity u_o and initial position x_o. The theory of the standard Brownian motion is obtained from this formalism in the particular case $F = 0$. It may be shown that eq. (7) is

$$W(u,t;u_o) = \left[\frac{m}{2\pi\kappa T(1-e^{-2\beta t})}\right]^{1/2} \exp\left(\frac{-m|u-u_o e^{-\beta t}|^2}{2\kappa T(1-e^{-2\beta t})}\right) \tag{7}$$

a gaussian distribution for the velocity u (at time t) with an average $u_o\, e^{-\beta t}$ and a standard deviation $\left[(1-e^{-2\beta t})\kappa T/m\right]^{1/2}$.

The probability distribution for the position coordinate x may also be derived. This satisfies the limits

$$\langle|x-x_o|^2\rangle \sim u_o^2 t^2 \qquad \text{for } t<<\beta^{-1} \tag{8}$$

$$\langle|x-x_o|^2\rangle \sim 6Dt \qquad \text{for } t>>\beta^{-1} \tag{9}$$

where the diffusion constant introduced has the value

$$D = \frac{\kappa T}{m\beta} = \frac{\kappa T}{6\pi a\eta} \tag{10}$$

For large times, $t>>\beta^{-1}$, the probability distribution of the position obbeys a simple gaussian distribution,

$$W(x,t;x_o,u_o) \sim \left(\frac{1}{4\pi Dt}\right)^{1/2} \exp\left(-\frac{|x-x_o|^2}{4Dt}\right), \text{ for } t>>\beta^{-1} \tag{11}$$

The vality of this theory has been confirmed experimentally, namely by Perrin[5] who observed the displacement of small grains (a = $= 2.1 \times 10^{-7}$m) in viscous solutions. The values of the Boltzmann constant thus obtained are consistent with those obtained by other methods. This provides a *a posteriori* validation of the Langevin equation.

In quite general terms, it may be shown[4] that the probability distribution in phase space W(x,u,t) satisfies the following partial differential equation - the Fokker-Planck equation

$$\partial_t W + u.\partial_x W + F.\partial_u W = \beta\ \partial_u \cdot (Wu) + \beta\ \frac{\kappa T}{m}\ \partial_u^2\ W \qquad (12)$$

The left-hand side of this equation contains the fluid-dynamics deterministic terms and the right-hand side the terms originating from the Brownian motion.

Eq. (12) is sometimes given the name of Chandrasekhar equation, the name of Fokker-Planck equation being reserved for the equation of motion of the probability distribution in velocity space W(u,t),

$$\partial_t W = \beta\ \partial_u \cdot (Wu) + \beta\ \frac{kT}{m}\ \partial_u^2\ W \qquad (13)$$

A last comment should be made about the Langevin equation (4). The dynamical friction ($-\beta u$) and the stochastic force A(t) have the same physical origin, namely the interactions of the system with a "heat-bath" assumed in thermal equilibrium. It is not unexpected, therefore, that they should be related. In fact they satisfy the relation

$$\beta = \frac{1}{6m\kappa T} \int_{-\infty}^{+\infty} dt\ \langle A(o).A(t) \rangle \qquad (14)$$

that is a particular example of the fluctuation-dissipation theorem.

2. BIOMOLECULAR REACTIONS

Frauenfelder[6] has been interested, and led a large research group for the last fifteen years, in the study of the dynamics of proteins and particularly the chemical reactions that occur in proteins. One of the processes that were studied more thoroughly is that of the binding of dioxigen to myoglobin (Mb). The process is obviously very complex as the dioxygen has to migrate from the

bulk of the solution up to an active site in the protein's interior before the actual binding can occur.

Myoglobin contains[7] about 150 aminoacids and has a molecular weight of about 18000; when folded (tertiary structure), it is globular and has a diameter of about 5 mm. The active center is protoheme (ferrous protoporphyrin IX). The O_2 (or CO) binds as an axial ligand to the heme iron. Myoglobin stores oxigen in muscles.

To study experimentally the binding process[8], the heme system with bound ligand is photodissociated by a flash from a dye laser; the subsequent rebinding is followed optically for times from 2μs to 1Ks. Mixtures of water with glycerol, sucrose, ethylene glycol and methanol were used to vary the solvent viscosity.

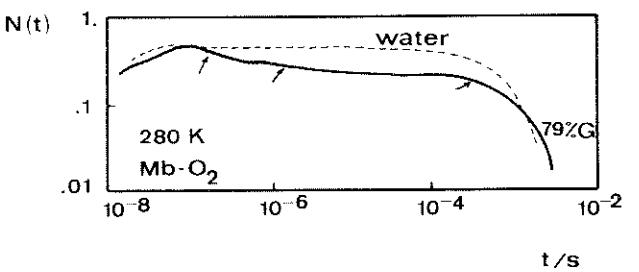

Fig. 4. Recombination of dioxigen to myolobin at 280K.
N(t) is the fraction of Mb molecules that have not rebound O_2 at time t. The initial rise is due to the photodissociation during the laser flash. In the subsequent decay, at least three processes with well separated characteristic times (signaled by the arrows) can be identified. (Adapted from ref.8.)

Before the flash, the ligand is bound at the heme iron, state A of scheme below

$$A \underset{k_{BA}}{\overset{k_{AB}}{\rightleftharpoons}} B \underset{k_{CB}}{\overset{k_{BC}}{\rightleftharpoons}} C \underset{k_{SC}}{\overset{k_{CS}}{\rightleftharpoons}} S$$

The photoflash breaks the bond and state B is formed. From there, the ligand may either recombine with the metal or migrate out through the protein into the solvent, S. Analysis of the coupled differential equations associated with the multi-step kinetics and fitting to the experimental data above lead to the calculated rates for the different steps at given temperature and solvent viscosity. The effect of the temperature on the rate may be felt directly

through an Arrhenius-type dependence and through a change of the solvent viscosity. The disentanglement of the two effects requires the collection of a large set of data taken at different temperatures and in different solvents.

Frauenfelder and co-workers have fitted the experimental data to a heuristically modified Kramers equation (eq. 2). They argued that the viscosity of the solvent is not felt directly at each barrier crossing inside the protein. In fact, while the outermost barrier seems[10] to be formed by the solvent, the innermost one must be originated by the heme and the middle one by the structure of the protein. Myoglobin has been shown[11] to have a solid like core and semiliquid regions towards the exterior. It is therefore reasonable to assume that, even inside the protein, the damping caused by the solvent will be felt but attenuated to some extent. It is assumed that

$$\beta_{internal} \propto \beta^k \propto \eta^k$$

The modified equation for step i → j is assumed to be of the form

$$K_{ij} = \left(\frac{A_{ij}}{\eta^{k_{ij}}} + A^{o}_{ij}\right) \exp(-H_{ij}/RT) \qquad (15)$$

TABLE 1

Parameters of the rate equation (15) for the multistep process $Mb + O_2 \rightleftharpoons MbO_2$ (Ref. 9)

Transition i → j	log A_{ij} (a)	log A^{o}_{ij} (b)	k	H^r/kJ mol^{-1} (c)
B → A	0	8.5	0	(9)
B → C	14.1	12.9	0.4	35
C → B	13.1	11.4		
C → S	13.1	(<10.5)	0.5	35
S → C	14.9	12.9		

(a) Units $s^{-1}M^{-1}(cp)^k$ for S→C and $s^{-1}(cp)^k$ for all other.

(b) Units $s^{-1}M^{-m}$ for S→C and s^{-1} for all other transitions.

(c) The assumption was made that $k_{ij} = k_{ji}$, $H^r_{ij} = H^r_{ji}$ but no marked changes appear if this constraint is released.

The problem of the attenuation of the solvent viscosity effect at barriers deep inside the protein has attracted the interest of several workers recently. Reichl[12] studied the diffusion in a multiwell potential with spatially varying viscosity and showed that information about solvent viscosities could be transferred to transition rates over internal barriers simply through boundary effects. Pursuing a different line, Hanggi[13] used a generalized Langevin equation formalism and showed that a particular frequency dependence of the dynamic friction could lead to a η^k dependence of the reaction rate.

3. MULTIMODAL THEORIES

In Kramers theory the chemical reaction process is described by a single coordinate. Using such a theory for a system as complex as a biomolecular reaction is obviously a very crude and risky approximation. Real systems do usually require a many-coordinate description and the coupling of the different modes may play an important role. In this section we shall examine certain consequences of these couplings and start by an introduction to general multiplicative noises, i.e., a type of fluctuating force that may appear in a mode as as consequence of additive stochastic forces in other modes coupled to it.

A. MULTIPLICATIVE NOISES

Let us consider the following autocatalytic reaction

$$A + X \underset{k_1'}{\overset{k_1}{\rightleftharpoons}} 3X$$

$$B + X \xrightarrow{k_2} C$$

and assume that the concentrations of A and B are kept constant, on average,

$$|A| = |A|^{\circ} + \delta_A \qquad \langle \delta_A \rangle = 0$$

$$|B| = |B|^{\circ} + \delta_B. \qquad \langle \delta_B \rangle = 0$$

we follow the concentration of $|X| = x$,

$$\frac{d}{dt}|X| = (k_1|A|^o - k_1'|B|^o)|X| - k_1'|X|^3 + (k_1\delta_A - k_1'\delta_B)|X|.$$

With the appropriate identifications, this equation may be written in the form

$$\dot{x} = d\,x - b\,x^3 + x\,F \tag{16}$$

where F represents the multiplicative fluctuating force with an intensity related to parameter Q,

$$\langle F(o)\,F(t)\rangle = Q\,\delta(t). \tag{17}$$

The stochastic differential equation (16) has been studied by Schenzle and Brand[14]. Its associated Fokker-Planck equation is

$$\partial_x P = -\partial_x\{(dx - b\,x^3 + \tfrac{1}{2}Q\,x)\,P\} + \tfrac{1}{2}Q\,\partial_x^2\,(x^2 P). \tag{18}$$

The steady state solution of (18) is

$$Po(x) = N\;x^{2d/Q-1}\;\exp(-\frac{b}{Q}\,x^2) \tag{19}$$

The most probable values of x is given by

$$\begin{cases} 0 & \text{if} \quad d \leqslant \frac{1}{2}Q \\ \sqrt{(d - \frac{1}{2}Q)/b} & \text{if} \quad d \geqslant \frac{1}{2}Q \end{cases} \tag{20}$$

which should be compared with the stationary solutions of the deterministic equation (F=o) associated with eq. (16), o and $\sqrt{d/b}$. We see that there is a change of regime induced by the intense multiplicative noise. When an additive noise of the usual kind is considered in eq. (16), the stationary distribution Po assumes a finite value at x = o even above the threshold values Q = 2d.

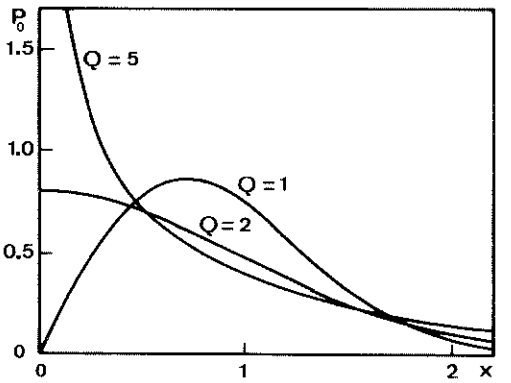

Fig. 5. Steady state solutions Po(x), eq. (19). Parameters were given the values d=1, b=1. The singularity at x=o that appears when Q>2d is suppressed when an additive noise is considered even if this is very weak[14].

B. COUPLING OF THE REACTION COORDINATE TO TRANSVERSE NORMAL MODES

In conventional theories of chemical reactions some sort of averaging is made, assuming that thermal equilibrium prevails in all but one coordinate. This is expected to be a crude approximation in many actual systems. In this section, we shall discuss two typical recent attemps to use more detailed models, one to bring in the effects of the solvent, the other to deal directly with a two--dimensional coupled system. Grote and Hynes[15] studied the coupling that may be induced by the solvent. Even in a simples reactive system like the triatomic process

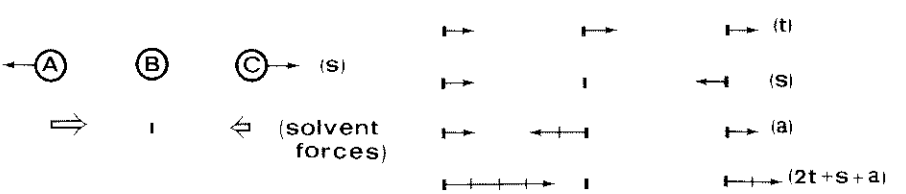

Fig. 6. Reaction AB + C ⇄ A + BC. The solvent forces induced by the symmetric vibration (assumed different due to the nature of atoms A and C) may induce a mixture of translation ant symmetric and asymmetric vibrations. The asymmetric vibration is the reactive mode.

in fig. 6, the sketch shows how the reactive and non-reactive modes may be coupled by the solvent.

Christoffel and Bowman[16] took another extreme view to introduce a coupled model. As a model for an isomerization reaction, they considered a 2-dimensional model potential inspired on that of amonia,

$$V(x,y) = \{\tfrac{1}{2} a x^2 + \tfrac{1}{2} b x^4 + V_o \exp(-c x^2)\} + \tfrac{1}{2} m [\omega_y(x)]^2 y^2 \qquad (21)$$

with

$$\omega_y(x) = \omega_o \{1-\lambda \exp(-\alpha x^2)\}. \qquad (22)$$

It has the form of a double-well oscillator coupled to a transverse harmonic mode. Both quantum-mechanical calculations and classical trajectory studies were performed.

At the adiabatic level of approximation, the problem is reduced to a 1-dimensional one with an adjusted potential, the shape of which depends on the energy of the transverse mode. As energy is pumped into this mode, a third well may be created in the region of the top of the barrier. This has drastic effects on the kinetics as new states may originate if the third well is sufficiently large. Fonseca et al.[17] extended the application of the coupling models to regions where the time scales are not so clearly separated. In this way, important corrections to the adiabatic approximation are obtained. Furthermore, the transmission of thermal fluctuations through the transverse mode causes interesting multiplicative noise effects.

A 2-dimensional potential similar to that of Christoffal and Bowman[16] was used[17].

$$V(x,y) = (V_o/a^4)(x^2-a^2)^2 + \tfrac{1}{2} [\omega_{eff}(x)]^2 y^2 \qquad (23)$$

$$= \phi(x) + \tfrac{1}{2} \omega_o^2 \sqrt{1-\psi(x)}\, y^2 \qquad (24)$$

with

$$\omega_{eff}(x) = \omega_o \{1-\lambda_{int} \exp(-x^2/r^2)\}^{1/2} \qquad (25)$$

The phenomenological equations of motion of the variables x, $\dot{x}$, y, $\dot{y}$ may be written

$$\dot{x} = v \tag{26}$$

$$\dot{v} = -\phi'(x) - \gamma\, v - \psi'(x)\, y^2 + f_1(t) \tag{27}$$

$$\dot{y} = w \tag{28}$$

$$\dot{w} = -\lambda w - y\, \psi(x) - y\, \omega_o^2 + f_2(t) \tag{29}$$

The random forces f_1 and f_2 are δ-correlated,

$$\langle f_i(o)\, f_j(t)\rangle = 2D_i\, \delta_{ij}\, \delta(t) \tag{30}$$

The complete Fokker-Planck equation may be written

$$\begin{aligned} \partial_t\, \rho(x,y,v,w,t) = \{ & -\partial_x + \phi'(x) + \tfrac{1}{2}\, \psi'(x)\, y^2\, \partial_v + \\ & + \gamma \left[\partial_v\, V + \langle v^2\rangle\, \partial_v^2\right] - \\ & - w\, \partial_y + y\, \psi(x)\, \partial_w + y\, \omega_o^2\, \partial_w + \\ & + \lambda \left[\partial_w\, w + \langle w^2\rangle\, \partial_w^2\right] \}\, \rho(x,y,v,w,t) \end{aligned} \tag{31}$$

but it is too complex to be solved directly. A special technique of adiabatic elimination[17] was used; this is a perturbational method that allows the introduction of corrections up to the desired accuracy. The variables of the problem are separated in two sets,

the variables of interest a
and the irrelevant variables b

and variables in one set are assumed to be only weakly compled to variables in the other set. Three time scales can be considered: τ_a, τ_b and $\tau_1 \approx 1/L_1$, the inverse of the coupling lagrangian between variables a and b, with the following relations

$$\tau_b \ll \tau_1$$

$$\tau_b \ll \tau_a .$$

A Zwanzig projection operator onto the space of variables a is defined so that any time dependence of variables b is projected out:

$$P\, \rho = \rho^{eq}(b) \int db\, \rho(a,b,t) . \tag{32}$$

The result of the elimination procedure on eq. (31) may be cast into

$$\partial_t \, P \, \tilde{\rho} = L_a \, P \, \tilde{\rho} + P \, L_1 \, P \, \tilde{\rho} + \int_o^t ds \; P \, L_1(t) \; (1-P) \; L_1(s) \; P \, \tilde{\rho}(s)$$

$$+ \text{(higher order terms in } \tau_b/\tau_1). \qquad (33)$$

This equation shows how the relevant part of ρ is driven by L_a and, indirectly (after extraction of the relevant part) by L_1. The last term (the first of the perturbation expansion) brings in an effect which is carried by the irrelevant variables from time s to time t.

At low friction, x and v cannot be separated and we must use $a = (x,v)$, $b = (y,w)$. The progress of the reaction may be measured by $\langle x \rangle$ or, in alternative, by the total population in one well. In the diffusional limit, x is the only relevant variable and then $a = x$, $b = (v,y,w)$. In this case, the adiabatic elimination discussed above allows a discussion of the importance of the standard adiabatic[16] terms compared with new terms that are now found to give large contributions to the reaction rate[17].

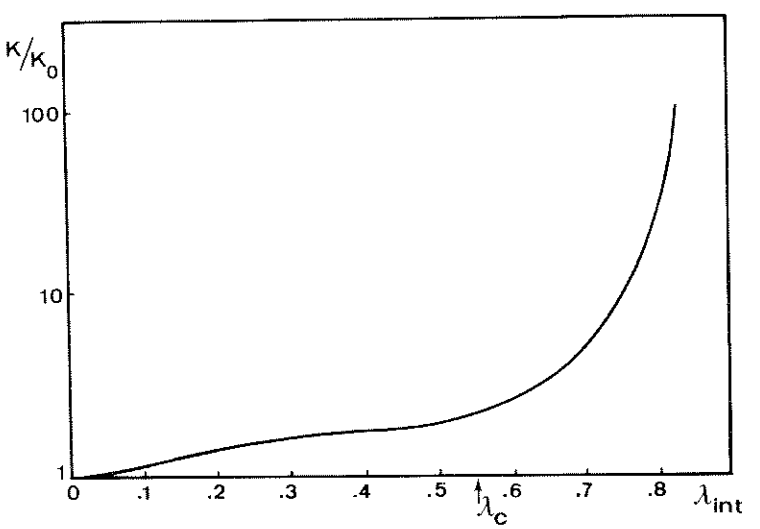

Fig. 7. Variation of the reaction rate with the coupling parameter. Parameters were given the values $V_o = 3.3\times10^{-7}$, $a = 0.183$, $r = 0.366$, $\langle v^2 \rangle = 2.0\times10^{-7}$, $\gamma = 1.0\times10^{-2}$, and $\langle v^2 \rangle \omega_o^2 = 85\times V_o$. The decay rate in the absence of interaction is $K_o = 30.0\times10^{-5}$. The threshold value of λ_{int} is $\lambda_c \approx 0.55$ (Adapted from ref. 17.)

Very interesting analytical results may be obtained for r>>a (long range of the coupling potential compared to the double well width - see eqs. 23 to 25). The equation of motion of the distribution of the position coordinate, $\rho(x,t)$, may be cast[17] into the form of eq. (18) which was studied by Schenzle and Brand[14]. As discussed in section A, above, there is a threshold value which is associated with a change of regime. This is well apparent in fig.7, where the calculated reaction rate is plotted against the intermodal coupling parameter of eq. (25).

To explore further into the low friction region where the time scales of x and v are similar, a first-passage time procedure[17] was devised. A change of variables, $(x,v) \rightarrow (x,E)$, is made and the problem is studied as one of slow diffusion on energy,

$$\partial_t \rho(x,E,t) = L^E \rho(x,E,t). \qquad (34)$$

The reaction rate is calculated as the inverse of the average first-passage time. The results of this calculation[17] are reproduced on the right-hand side of fig. 8.

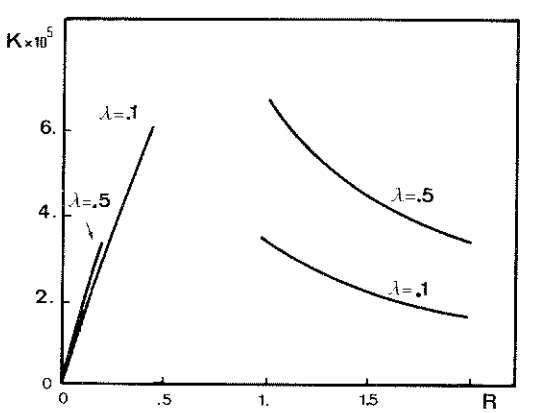

Fig. 8. Variation of the reaction rate with viscosity of the medium. The variable on the abscissae is $R = \Gamma_V/\gamma = \omega_o^2/\lambda\gamma$. The curves on the left-hand side were obtained using a continued-fraction procedure[18] to solve eq. (33); those on the right-hand side were calculated by a first-passage time technique. Parameters were given the values $V_o = 2.\times10^{-7}$, a = 0.5, r = 1.0, and $\langle y^2\rangle\ \omega_o^2 = \langle v^2\rangle = \langle w^2\rangle = 1.0\times10^{-7}$. (Adapted from results in ref. 17.)

The results obtained are interpreted as a synergism of inertia and multiplicative noise. Indeed, the fluctuations in the transverse mode become ineffective near the top of the barrier so that inertia is essential for it to be overcome. When figs. 8 and 3 are compared, it is clear that the complex program of research described above gives a computational confirmation of the general qualitative features initially predicted by Kramers. In the detail, interesting new effects are found where the multiplicative noise plays a crucial role.

ACKNOWLEDGEMENTS

I greatly benefited from discussions with Dr. Paolo Grigolini and Dr. Fabio Marchesoni of the University of Pisa(Italy) and Teresa Fonseca of the University of Porto(Portugal). This work was supported, in part, by INIC(Lisbon) and CNR(Rome).

REFERENCES

1. H. A. Kramers, Physica 7, 284,(1940).
2. S. Chandrasekhar, Rev.Mod.Phys., 15, 1, (1943).
3. R. F. Grote and J. T. Hynes, J.Chem.Phys., 77, 3736, (1982).
4. D. A. McQuarrie, *Statistical Mechanics*, (Harper & Row, New York, 1976). chap. 20.
5. J. Perrin, *Atoms*, (Constable, London, 1916).
6. P. G. Debrunner and H. Frauenfelder, *Experiences in Biochemical Perception*, (Academic Press, New York, 1982), chap. 25.
7. R. H. Austin, K. Beeson, L. Eisenstein, H. Frauenfelder, L.Gunsalus, and V. P. Marshall, Phys.Rev.Lett., 32, 403, (1974).
8. D. Beece, L. Eisenstein, H. Frauenfelder, D. Good, M. C. Marden, L. Reinisch, A. H. Reynolds, L. B. Sorensen and K. T. Yue, Biochem., 19, 5147, (1980).
9. D. Beece, L. Eisenstein, H. Frauenfelder, D. Good, M. C. Marden, L. Reinisch, A. H. Reynolds, L. B. Sorensen and K. T. Yue, in *Hemoglobin and Oxygen Binding* (ed. Chien Ho), (Elsevier North Holland, 1982), 363-369.
10. N. Alberding, R. H. Austin, S. S. Chan, L. Eisenstein, H. Frauenfelder, I. C. Gunsalus, and T. M. Nordlund, J.Chem.Phys., 65, 4701, (1976).
11. H. Frauenfelder, G. A. Petsko, and D. Tsernoglu, Nature, 280, 558, (1979).
12. L. E. Reichl, J. Chem. Phys., 17, 4199, (1982).
13. P. Hanggi, J. Stat. Phys., 30, 401, (1983).
14. A. Schenzle, and H. Brand, Phys. Rev., 20A, 1628, (1979).
15. R. F. Grote, and J. T. Hynes, J. Chem. Phys., 74, 4465, (1981); ib., 75, 2191, (1981).
16. K. M. Christoffel, and J. M. Bowman, J. Chem. Phys., 74, 5057, (1981).
17. T. Fonseca, J. A. N. F. Gomes, and P. Grigolini, Int. J. Quantum Chem., 23, 473, (1983); T. Fonseca, J. A. N. F. Gomes, P. Grigolini, and F. Marchesoni, J. Chem. Phys., in press; ib., submitted.

18. M. Giordano, P. Grigolini, and P. Marin, Chem. Phys. Lett., 83, 554, (1981); T. Fonseca, P. Grigolini, and P. Marin, Phys. Lett. A88, 117, (1982); F. Marchesoni, P. Grigolini and P. Marin, Chem. Phys. Lett., 87, 451, (1982); S. Faetti, P. Grigolini, and F. Marchesoni, Z. Zhysik E, 47, 353, (1983).