OVERVIEW AND COMMENTS ON RATE PROCESSES

I. SIMULATIONS OF RATE PROCESSES

Ghosh and McCammon (1987) and Karplus and coworkers in previous work described quantitatively the barrier traversal for Tyr-35 isomerization of BPTI.

In the demonstration, we showed movies of the motions of Tyr-35 and other atoms of BPTI at equilibrium (equivalent for Tyr-35 to motions associated with the reactant well of the isomerization). It is likely that the dynamics of Tyr-35 at the barrier top are qualitatively similar to those at the well bottom, in being diffusive and in being correlated with motions of other parts of the structure.

The simulations of Ghosh and McCammon together with the trajectories shown in the demonstration give a picture of the complex dynamics of barrier traversal.

This picture should apply generally, to protein reactions in which there are Angstrom-level movements of the structure (ES complex isomerizations, etc.).

Diffusive dynamics implies that there are two time scales, τ_{MIC} and $\tau_{BROWNIAN}$. For reaction dynamics, two additional characteristic times need be considered, that for barrier-top traversal, $\tau_{BARRIER}$, and that of the chemical reaction, τ_{RXN}.

Motions on the time scales of τ_{MIC} and $\tau_{BROWNIAN}$ could be distinguished in the trajectories of BPTI and the *alpha* –helix. Which motions?

II. THEORIES OF RATE PROCESSES

1. COLLISION THEORY (not discussed)

kinetic theory of gases.

2. TRANSITION STATE THEORY (TST)

Simple model - "done" fully in class; widely and successfully used; the first modern reaction rate theory; one has a duty to understand TST.

TST has some unusual, even nonphysical, assumptions.

3. KRAMERS THEORY

The theory has a standard and proper physical foundation and development.

It treats solvent effects & reactions in a dense medium; static (equilibrium) effects - TST ok; dynamic effects - beyond scope of TST.

Kramers theory needed to account for collisions between solvent and activated complex that reduce rate of passage over barrier.

4. TIME CORRELATION FUNCTIONS (TCF)

essentially same model as Kramers theory.

more general theoretical framework (TCF).

treat time-dependent friction, particularly the case of high, sharp barriers, for which Kramers theory fails.

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SHOULD HAVE FEELING FOR ....

1. How the picture of a protein reaction, from the simulations, relates to theories of rate processes and the models behind them (e.g., there is an obvious tie to Kramers theory).

2. How the theoretical understanding of rate proce3sses has evolved:

(collision ->) TST -> Kramers -> TCF -> ???

3. The scope of the various theories, i.e., when they apply.

Why does TST do so well, considering its flawed underpining?

4. A model (or theory) is not a completely accurate description of reality (experiment). IT IS NOT INTENDED TO BE. A model is successful if it leads to new understanding and insights. A model necessarily abstracts one or a few of the most significant features of a process:

TST - barrier height, 1 control of rate Kramers - diffusion and solvent effects, in addition to barrier height Hynes - barrier shape, in addition to above; remove restriction of constant f from Kramers picture

3 4. The understanding of rate processes relevant to biochemistry is incomplete. For example, not yet adequately considered are:

a) time scales: tBrownian -> treaction rate, with regard to:

gating;

coupling of dihedral transitions to dynamics along the reaction coordinate.

b) the complexity of the transverse coordinate dynamics, which are integrated to obtain the friction f, deserve more careful treatment to resolve specific motions crosscorrelated with barrier traversal.

c) a time range of .1 - 1 ps for barrier traversal is that for maximally dissipative dynamics, which means, more plainly, that the crosscorrelations of the transverse motions are maximally complex, and that the barrier traversal is not along a minimum energy barrier (adiabatic path).

4 WHAT IS IMPORTANT TO KNOW?

1. The picture from the MD simulations of barrier traversal in the isomerization of Tyr-35 of BPTI. This should be the reference point you carry with you, for thoughts about the dynamics and mechanism of action of enzymes and other biomolecules.

2. TST - the model and the assumptions; why it remains an important theory; the meaning of $k2 = kT/h$ .... and how it relates to $k = wR/2p$ ....

3. Kramers theory - model and assumptions; how these differ from TST and are similar to TST; how result reduces to TST; what k represents; dynamic solvent effects; Langevin equation; the friction.

4. Hynes - model and assumptions; differences and similarities to Kramers

model; why important.

5. What the several time scales are and how they are constrained by the assumptions of the several theories (and constrain the scopes of the theories).

6. Scopes of the various theories.

7. The use of a model to focus on one element of a complex problem, and so derive insight.