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Gas-Phase Ionic Reactions: Dynamics and Mechanism of Nucleophilic Displacements

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Nucleophilic displacement reactions (the S_N2 reaction) of ions in the gas phase are a prototypical reaction system that allows a study of dynamics, mechanisms, and structure-energy relations. This article reviews aspects of the kinetics (especially the applicability of statistical reaction rate theory), the relation of structure and reactivity, and the effects of small numbers of solvent molecules on the reaction and compares the behavior of the ionic reaction in the gas phase with that in solution.

The study of reaction mechanisms plays an important role in chemistry. By understanding the details of the pathways and structural effects in reactions, chemists not only learn how to control them to obtain products of interest, but also discover and invent new chemistry. Ions are used extensively in organic reaction chemistry as reactants, intermediates, and catalysts because they are highly reactive. The solvation energies of ions can be very large, often hundreds of kilocalories per mole, so differences in solvation energy can easily mask differences in intrinsic reactivity between similar species (*1*). Thus, by studying ionic reactions in the gas phase, without solvent, we can learn about the intrinsic behavior in ionic reactions and thereby expose the role of the solvent. Furthermore, by studying the effect on these reactions of adding solvent molecules one at a time (microsolvation), we can learn how reaction dynamics and potential energy surfaces (PESs) change with increasing solvation.

In this overview, we concentrate on the S_N2 reaction, $X^- + RY \rightarrow RX + Y^-$, as a representative reaction involving ionic species. It has been widely studied and is an important reaction for interchanging functional groups and for forming carbon-carbon bonds or activating the molecule for this purpose. We have drawn extensively from our own work, as in a review of this length it is impossible to do justice to all of the important, recent organic mechanistic work from other laboratories (*2–5*) .

The PES for gas-phase S_N2 reactions is now widely believed to be a double-well potential (*1*), in contrast to the situation in solution (*6*) (Fig. 1). The transition state for the S_N2 displacement step (k_2 in Fig. 2) has a tighter configuration and thus entropically less favorable than the transition state for formation or dissociation of the complex (k_{-1} in Fig. 2), so reactions that proceed with measurable rates must typically have transition state energies for the displacement step that lie below the energies of the reactants. Because the energies of intermediates and transition states lie below the energies of the initial reactants, and because gas-phase reactions are often best carried out at low pressure where the intermediates cannot be stabilized, the determination of the transition state energy is more difficult than is the case in solution. Early studies showed that when a complex was formed between methyl chloride and a chloride ion, the chloride that was added could be transferred to another neutral molecule, whereas the chloride in the methyl chloride retained its identity and was not transferred (*7*). Although these halide–methyl halide complexes correspond to intermediates in reactions, the barrier to reaction is sufficiently high that they are effectively unreactive in the displacement process. Recently, it has been possible to characterize S_N2 reactions more completely. Both reactant and product complexes in unsymmetrical reactions have been isolated and shown to be different (*8*, *9*), and it has been possible to activate the reactant complex with infrared multiple photon irradiation (*8*) or by collisions (*9–11*) and complete the reaction. In addition, Dessent and Johnson have cooled the S_N2 ion-dipole complex in a supersonic expan-

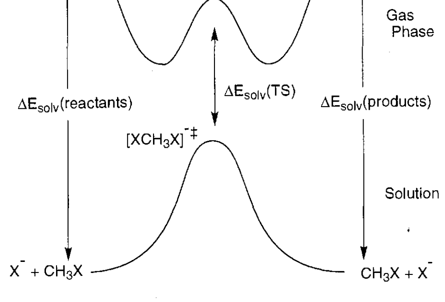

Fig. 1. Gas-phase and solution PES for the S_N2 reaction.

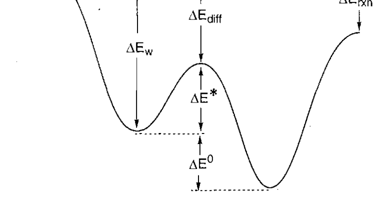

Fig. 2. PES for a generic gas-phase S_N2 reaction.

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sion, allowing structural characterization with negative ion photoelectron spectroscopy (*12*). They have also succeeded in triggering the ground-state reaction from the stabilized complex through photoexcitation of the diabatic (Evans-Polanyi) electronically excited states (*13*).

A number of issues involving the gas-phase ionic S_N2 reaction are currently being studied, and we address some of them here. Do these reactions obey statistical reaction rate theory? How does solvation affect the dynamics of these reactions, and what is the effect of adding solvent molecules one at a time (microsolvation)? What structure-energy relations can be found in the gas-phase reactions, and what generalizations can be made about the S_N2 reaction?

Kinetics

Thermodynamic information about the endpoints and intermediate complexes of gas-phase S_N2 reactions is often obtained from direct measurement of an equilibrium constant, either from exchange reactions (*14*) or in a high-pressure mass spectrometer (HPMS) (*5*, *9*). Although some activation energies have been determined from Arrhenius-type behavior in HPMS studies (*5*, *9*), the energy of the transition state is usually inferred from gas-phase kinetics at low pressures, where the absence of thermalizing collisions leads to nonequilibrium energy distributions. A microscopically rigorous characterization of the reaction kinetics requires a detailed molecular dynamics study, a costly and time-consuming exercise.

The gas-phase kinetic data can be interpreted simply by using the scheme in Fig. 2, if a few assumptions hold. If we assume that the minimum-energy reactant complex $X^-{\cdot}CH_3Y$ (Fig. 2) is a true reactive intermediate in essentially all collisions (that is, contributions from direct reactions and nonreactive elastic scattering are negligible), then the rate constant for formation of the intermediate is the classical collision rate constant, k_1, between the reactants and is easily calculated (*15*). To understand the overall reaction kinetics we need only understand the kinetics of the intermediate (*16*)—how often it reacts to give the product complex, k_2, or dissociates to regenerate reactants, k_{-1}.

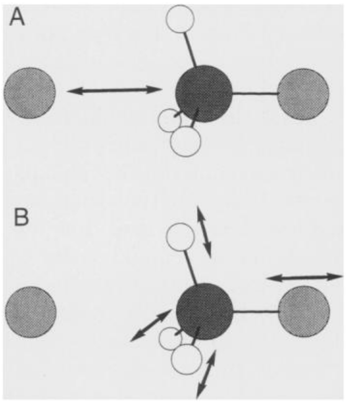


Fig. 3. Vibrational modes in S_N2 complexes: (**A**) intermolecular modes, (**B**) intramolecular modes.

The kinetics of the intermediate are straightforward if energy redistributes on the time scale of the reaction and if a transition state can be properly defined (*17*). The dynamics of a system in which these two assumptions hold are often said to be "statistical"; k_2 and k_{-1} can be determined by calculation of the partition functions at the transition states of interest, a far more convenient recourse than detailed microscopic dynamics.

Purely statistical behavior is one limit of possible reaction dynamics; at the other limit the reaction outcome is very sensitive to the initial reactant state. The actual reaction dynamics of most systems fall somewhere between these two limits, and understanding where a reaction is on that spectrum is essential to a proper interpretation of experimental results. Ion-molecule reactions generally approach the limit of statistical behavior because the deep well of the reactant complex on the PES enables formation of a relatively long-lived intermediate in which energy redistributes before reaction. Statistical theories have been used successfully to explain the single-collision kinetics of many S_N2 systems, and the PESs obtained from these analyses generally agree with those from HPMS (*9*, *11*, *18*) or theoretical (*19*) studies.

Recent work has shown that although many S_N2 reactions can be treated statistically, selected systems behave nonstatistically to the extent that direct dynamics need to be considered when interpreting experimental observations (*20–23*). Dynamics calculations by Hase and co-workers (*20*) have shown that some S_N2 trajectories cross the barrier but then return to the reactants by recrossing the barrier (in violation of transition state theory), leading to reduced reaction rates.

Another source of nonstatistical behavior involves energy redistribution in certain S_N2 intermediates before and after the reaction. Examples include the reactions of Cl^- + CH_3Br (*21*, *24*) and Cl^- + CH_3Cl (*23*, *25*). In particular, there is a dynamic bottleneck to energy transfer between what Hase refers to as inter- and intramolecular modes (*20*) of the reactant complex (Fig. 3). The intermolecular modes of the complex are closely related to the translational and rotational modes of the reactants in complex formation and dissociation, whereas intramolecular modes are related to molecular vibrations, which are necessary for crossing the S_N2 transition state. A significant bottleneck to energy transfer, therefore, means that the initial location of energy can have a profound effect on the outcome of a collision. Indeed, the intermediates in the reaction of Cl^- + CH_3Br have been shown to be less likely to react when they are formed with predominantly intermolecular energy rather than intramolecular energy (*21*). Other evidence for poor energy transfer includes product complexes of exothermic S_N2 reactions that dissociate with over 50% of the reaction exothermicity trapped in vibrational modes of the product complex (*11*, *26*, *27*), and a vibrationally excited S_N2 intermediate that reacts at least four times as often as is predicted from statistical theory (*28*).

Those S_N2 systems that exhibit nonstatistical dynamics share similar characteristics. They are very small or sufficiently energetic that their reaction rate constants, k_2, are on the order of 10^{11} s^{-1} or greater. Reaction time scales of tens of picoseconds and less are sufficiently short that they start to approach the periods of rotations or intermolecular vibrations of the dissociating ion-dipole complex. Because there is not enough time to redistribute energy efficiently between the intra- and intermolecular modes, these reactions clearly cannot be treated statistically.

S_N2 reactions for larger molecules, such as cyano- or benzyl-substituted alkyl chlorides, appear to follow statistical behavior (*29*, *30*). The expected lifetime of the intermediates in these systems is greater than 10^{-8} s, and energy transfer between the intra- and intermolecular modes is therefore efficient. Most S_N2 reactions that are structurally complex enough to offer insights into organic reaction mechanisms should also proceed through intermediates that are similarly long lived (*31*). Thus, although the gas-phase S_N2 reactions of small or highly energetic systems provide an opportunity to study the fundamentals of microscopic organic reaction dynamics, the dynamics of larger systems are sufficiently characterized by the simplifying assumptions of statistical theories that their intrinsic reactivities can be readily discerned.

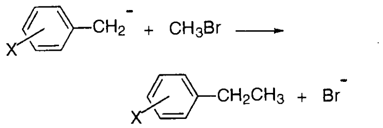
Structure and Energetics

Much of mechanistic chemistry is devoted to understanding the effects of structure and energetics on reactivity (*32*), and models have been developed to explain these effects in S_N2 reactions (*13*, *33*). The solution-phase S_N2 reaction has been studied extensively (*34*), but interpretation of the results is complicated by the effects of solvation. By studying the S_N2 reaction in the gas phase, intrinsic relations between structure and energetics are revealed. Experimentally, these relations have been determined through interpretation of kinetic data or the direct observation of intermediates on the S_N2 PES (*8*, *9*).

Identity exchange reactions are often too slow to be measured experimentally, so most studies of the effect of structure on reactivity have been carried out with exothermic reactions (*35*). It is then necessary to distinguish the effect of a thermodynamic driving force on the PES from the intrinsic kinetic effect under study. The actual displacement process, k_2, of gas-phase S_N2 reactions can be treated as a unimolecular isomerization of the reactant ion–molecule complex to form the product complex (Fig. 2). Marcus theory has been applied to a variety of unimolecular reactions and is therefore well suited for study of S_N2 reactions. Extension of Marcus theory to gas-phase S_N2 reactions has allowed separation of the activation barrier, ΔE^*, into its kinetic and thermodynamic components. In the Marcus equation (Eq. 1), ΔE_o^* is the intrinsic activation energy (*36*), and ΔE° is the exothermicity (Fig. 2) (*37*, *38*).

$$\Delta E^* = \Delta E_o^* + \Delta E^\circ/2 + [(\Delta E^\circ)^2/16\Delta E_o^*] \quad (1)$$

In a quantitative study of Marcus theory for the S_N2 reactions of a series of substituted benzyl anions with CH_3Br (Eq. 2), the reaction efficiency varied with the exothermicity as predicted by Eq. 1 (*39*).



(2)

For an exothermic exchange reaction, ΔE_o^* does not correspond to the energy of a physical transition state because there is no true thermoneutral analog. However, the S_N2 transition state is likely to have some of the character of each of the two corresponding identity exchange reactions. It is reasonable, then, that the intrinsic barrier ΔE_o^* should be near the mean of the barriers of the exchange reactions (Eq. 3). This assumption, the Marcus additivity postulate, makes it possible to quantify all of the individual contributions to S_N2 activation barriers in terms of independently determined quantities: reaction exothermicity and barriers to self-exchange reactions (*40*). The validity of the additivity postulate in S_N2 reactions has been demonstrated experimentally with X and Y = Cl, Br and R = phenyl, CN (Eq. 4) and theoretically from quantum calculations by Wolfe, Mitchell, and Schlegel (*41*, *42*).

$$\Delta E_o^*(X,Y) = 1/2[\Delta E_o^*(X,X) + \Delta E_o^*(Y,Y)] \quad (3)$$

$$X^- + RCH_2Y \rightarrow RCH_2X + Y^- \quad (4)$$

The Marcus approach makes it possible to quantify "fuzzy" ideas like anion nucleophilicity, which is difficult to discern from reactions with different entering and leaving groups. Reactions with many nucleophiles may simply be fast because they are very exothermic. According to the additivity postulate, each group contributes to the activation barrier. Pellerite (*43*, *44*) suggested that a good measure of the nucleophilicity of X^- is the intrinsic activation energy for the identity reaction $X^- + CH_3X \rightarrow XCH_3 + X^-$, obviating the problems of different entering and leaving groups. The Marcus additivity postulate was used to determine ΔE_o^* for a series of identity exchange reactions (*44*). Halides, for example, whose identity exchange reactions are relatively fast, were found to have a greater intrinsic nucleophilicity than alkoxides, which only react at a measurable rate in exothermic reactions. The intrinsic nucleophilicity of X^- was found to correlate with the heterolytic bond dissociation energy (Eq. 5), indicating that the S_N2 transition state has significant charge separation.

$$CH_3X \rightarrow CH_3^+ + X^- \quad (5)$$

The nature of the transition state has also been examined in a study of intrinsic polar effects. It has been shown for identity halide exchange reactions (Eq. 6) that α substituents such as R = benzyl, allyl, and cyano stabilize the S_N2 transition state, resulting in a larger value of ΔE_{diff} (Fig. 2) and increased reaction efficiencies by up to four orders of magnitude (*19*, *29*). Equilibrium studies show that the α substituents stabilize the ion-molecule complex by a nearly identical amount. The value of ΔE^* is therefore independent of the α substituent for these reactions. Thus, the charge distribution in the transition state is essentially identical to that in the ion-dipole complex, and resonance interactions in the transition state are unimportant.

$$^{37}Cl^- + RCH_2Cl \rightarrow {}^{37}ClCH_2R + Cl^- \quad (6)$$

Steric effects of both the substrate and nucleophile on S_N2 reactivity have been studied (*4*, *5*, *9*, *18*, *45*, *46*). Because most thermoneutral reactions are slow, the relative rates of a series of exothermic reactions have been compared (*4*). Unfortunately, their use is limited because alternate pathways such as elimination or proton transfer may compete and become faster than the S_N2 pathway as the exothermicity increases. Reactions of α-cyano alkyl halides are fast enough that identity exchange reactions can be used to study intrinsic steric effects. Adding a methyl group to chloroacetonitrile decreases the rate of the identity exchange reaction by a factor of 30 (*47*). These initial studies suggest that the energetic effect of steric encumbrance in the gas phase is similar to that in the condensed phase.

Microsolvation

In the gas phase, the S_N2 reaction barrier frequently has a lower potential energy than the reactants, but in the condensed phase the barrier is higher than the reactants (*6*) (Fig. 1). The origin of the additional barrier in solution can be understood by consideration of a simple Born solvation model (*48*). The charge in the transition state is delocalized over a larger area than in the nucleophile and is therefore less easily solvated. In addition to the static dielectric effects of the solvent, the dynamics of solvent motion during the reaction must be considered. Theoretical analyses by Hynes *et al.* (*49*) and Marcus (*38*) have shown that coupling between the solvent and reactants can have substantial effects on condensed-phase reactions.

Microsolvated reactions, in which one or more solvent molecules have been complexed to the nucleophile in the gas phase, have been used as a model to attempt to understand solvation effects on reactivity (*50*–*52*). The thermodynamic stabilization of ions by solvent molecules, such as water, has been widely studied by equilibrium methods (*14*, *53*). For example, the binding energy of water to a chloride ion is 15 kcal/mol, with the addition of a second water molecule further stabilizing the complex by another 12 kcal/mol (*54*). Solvation of the transition state cannot be studied by equilibrium techniques, but it can be examined by analysis of kinetic data and by computational methods.

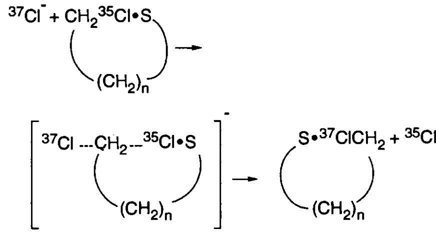
For one of the simplest microsolvated S_N2 reactions, $Cl^-{\cdot}H_2O$ with CH_3Cl (Eq. 7), ab initio molecular orbital calculations demonstrate that the transition state is stabilized less than Cl^-, and thus the barrier to reaction is increased relative to that of the unsolvated reaction (*55*, *56*). Tucker and Truhlar have used a computed PES to perform transition state calculations, which predict that the reaction will be more than a 1000 times slower than the unsolvated reaction (*57*). A comparison of a nonequilibrium kinetic model, where the degrees of freedom of water participated in the reaction coordinate, to an equilibrium model, where they did not, showed that nonequilibrium effects only contributed ~10% to the rate constant despite the strong coupling of the solvent and nucleophile (*57*). This demonstrates that the strength of the solvent interaction may not indicate how important nonequilibrium effects will be.

$$^{37}Cl^- \cdot (H_2O)_n + CH_3{}^{35}Cl \rightarrow CH_3{}^{37}Cl + {}^{35}Cl^- \cdot (H_2O)_n \qquad (7)$$

To best study microsolvated reactions, the unsolvated reaction must not be controlled solely by the collision rate. The reaction cannot be too slow, however, or the microsolvated reaction will then become too slow to measure. Identity exchange reactions, such as Cl^- with CH_3Cl, are typically too slow (*58*) to have measurable rates when microsolvated. One solution to the problem is to study exothermic reactions that have measurable efficiencies when microsolvated. Studies by Bohme (*59*) and Hierl *et al.* (*51*) showed the effect of stepwise water solvation on the reaction of OH^- with CH_3Cl. One water molecule slowed the reaction by a factor of ~2, and two molecules slowed the reaction by a factor of ~1000. Study of additional solvent molecules was limited by the inability to measure increasingly slower rates. Recently the reaction rates of $F^- \cdot H_2O$ with methyl halides have been measured (*3*). The reaction with CH_3Cl slows by a factor of ~100 relative to the unsolvated case, whereas the reactions with CH_3Br and CH_3I decrease only by a factor of ~2. For these systems, the unsolvated reaction is collision controlled, which complicates interpretation of the effect of the solvent on the transition state.

Exothermic microsolvated reactions produce both solvated and unsolvated products. The unsolvated product arises when reactions are sufficiently exothermic to "boil off" the solvent molecule during the reaction. For example, the reaction of $OH^- \cdot H_2O$ with CH_3Cl produces both Cl^- and $Cl^- \cdot H_2O$. Interestingly, no $Cl^- \cdot CH_3OH$ was observed (*51*, *59*), although this channel is equally exothermic as the production of $Cl^- \cdot H_2O$. The experiments do not reveal whether the solvent molecule is transferred to the product and then lost or whether there are dynamic problems with solvent transfer to the product. Calculations on the reaction path of $F^- \cdot H_2O$ with CH_3Cl suggest that the solvent transfer occurs after the dynamic bottleneck of the halide transfer step (*60*). Further experimental and computational studies are needed to unravel the complex dynamics of these reactions.

Craig and Brauman (*61*) used a different approach to study solvation by examining Cl^- identity exchange reactions where an alkyl chain with a polar group, S, was covalently attached to the reaction center (Eq. 8, S = CN, OH). The stabilities of both the transition state and the ion-molecule complex were found to be sensitive to the length of the alkyl chain, but they did not correlate with each other. This is consistent with the different geometries of the transition state and the ion-dipole complex and indicates that the transition state is "solvated" differently than is the ion-molecule complex.



(8)

For a microsolvated reaction to best mimic solution-phase behavior, the solvent molecule should follow the entire reaction. That is, the reactant, product, and transition state should all experience the effects of the solvent molecule. The microsolvated S_N2 reactions that have been studied do not have this characteristic and are therefore not the optimal models for understanding solvent effects. Other microsolvated reactions where the solvent molecule is fully transferred from reactant to product may be more convenient for study (*62*).

Outlook

Our insights into the details of the mechanisms of ionic reactions have been enhanced significantly by studies in the gas phase. We have learned a great deal about the gas-phase reactions themselves and also about their solution counterparts. The work has stimulated both theory and experiment in the gas phase and in solution. We are now in a position to ask detailed mechanistic questions about other reaction systems and to test more completely the conditions under which various dynamic models, especially statistical ones, are valid. Continued development of ion sources such as electrospray and laser-induced desorption will present an array of new structural types of ions to be studied. New photon sources both in wavelength and in time domain will expose processes in more detail. Energy control of ions and neutral molecules will allow a more comprehensive view of dynamics. The future should also bring more insights into the nature and effect of microsolvation on the dynamics of these reactions.

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Chemical Dynamics in Proteins: The Photoisomerization of Retinal in Bacteriorhodopsin

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Chemical dynamics in proteins are discussed, with bacteriorhodopsin serving as a model system. Ultrafast time-resolved methods used to probe the chemical dynamics of retinal photoisomerization in bacteriorhodopsin are discussed, along with future prospects for ultrafast time-resolved crystallography. The photoisomerization of retinal in bacteriorhodopsin is far more selective and efficient than in solution, the origins of which are discussed in the context of a three-state model for the photoisomerization reaction coordinate. The chemical dynamics are complex, with the excited-state relaxation exhibiting a multiexponential decay with well-defined rate constants. Possible origins for the two major components are also discussed.

The chemistry of life as we know it requires a myriad of enzyme-catalyzed reactions, all of which take place in the condensed phase. These reactions proceed with remarkable efficiency and selectivity, the likes of which are rarely duplicated in nonbiological systems. The key difference lies in the solvent. In biological systems, the "solvent" surrounding the active site is often a highly organized protein whose architecture influences the chemical behavior at the active center. Moreover, that architecture can provide docking sites to house intermediates involved in the reaction and can create species-selective passageways between the active site and the surrounding solution. The structure of a protein, therefore, tailors its function. Static structures determined at atomic resolution can reveal the relative proximity and orientation of functional groups and can help to rationalize a protein's chemical behavior; however, to be able to predict its chemical behavior, we must understand the influence of its architecture on its chemical dynamics. This insight may allow the design of new protein sequences that fold into target structures and execute a designed function and may also help to assess the function of proteins that will be discovered as a consequence of sequencing the human genome. Generating this level of understanding will require contributions from molecular dynamics, quantum mechanics, molecular biology, and time-resolved spectroscopy and crystallography. The rapid pace of advances among these methods is pushing this goal ever closer to reality.

In the context of this article, "chemical dynamics" relates to the pathway by which chemical bonds are broken and formed. The breaking and making of bonds renders the process "chemical," and the term "dynamics" hints at the fact that the dominant outcome corresponds to the fastest of several possible pathways. A detailed understanding of chemical dynamics requires knowledge of both electronic and nuclear motion along the predominant reaction pathway and is often summarized in the form of a simple potential energy surface that depicts the putative reaction pathway as well as its associated dynamics.

Whether occurring within a protein or in the gas phase, chemical transformations proceed on the femtosecond time scale. Consequently, direct investigations into chemical dynamics require methods that provide femtosecond time resolution. Currently, all such methods are pump-probe techniques, where an ultrashort pulse of light excites a chromophore and triggers the process to be investigated. The pump-probe approach, therefore, constrains the experimental study of chemical dynamics in proteins to photobiological systems (such as the rhodopsins, the photosynthetic reaction center, photoactive yellow protein, and phytochrome) or to proteins that can be optically triggered (for example, the photodetachment of ligands from ligand-binding heme proteins). Nevertheless, incisive experimental characterization of chemical dynamics in a small number of photoactive proteins should provide sufficient constraints with which to test and refine general theoretical models of chemical dynamics in proteins.

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