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Conformational Populations and Reaction Rates

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The overall rate constant k for a reaction that involves multiple reaction channels is given by the expression $k = (1/D)(k_1 + k_2 + ...)$ with the k_i values computed for each transition state but with each referenced to a single reactant state, conveniently that having the lowest free energy of formation. D is the Boltzmann denominator. Product distributions are governed by the free energies of formation of the several transition states (the Curtin principle). However, the $1/D$ term makes k dependent on energy levels of reactant states as well. For one study of esterification the corrections to log k ranged from −0.25 to +0.25 for log k based on global minima alone. In that study the correction was significant since the standard deviation of log k_{calc} was 0.24.

Relative rate constants of reactions controlled primarily by steric effects may be estimated by molecular mechanics.[1-28] Double differences of steric energies of reactants and of models of transition states are assumed to equal double differences of enthalpies of activation. The calculations pertain to the gas phase and to single conformers. It is assumed that solvation effects cancel in the double differences, and it is usually assumed that entropy effects also cancel, although entropies were explicitly estimated for cyclization reactions.[11] Details of the underlying principles have been described elsewhere.[10,12,29] Since steric energies are force field dependent, it is better to use formal steric enthalpies instead.[29-31] The results have been highly encouraging; relative rate constants are reproduced well.

The calculations depend on locating the conformer of lowest energy, the global minimum for each reactant and for the corresponding model of the transition state. This is a nontrivial problem, but calculations are biased unless the minima have been correctly identified. Most molecules exist in a mixture of conformers at the temperature of the reaction, and there may be several conformers of the transition state model. The question I now address is the proper method for taking account of conformer populations of reactants and of multiple conformers of transition states, which provide multiple reaction channels. The results have general applicability. Reactions that occur by multiple channels are of considerable current interest in other connections.[32] A classical example is the Winstein and Holness treatment of reactions of axial and equatorial cyclohexanol derivatives.[33] Recent examples of W–H and of the related Curtin principle[34] are the extensive studies of Seeman and of Viers and of their co-workers on the Menschutkin reactions of nicotine and related amines.[35-40]

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The W–H principle and the Curtin principle are concerned with product distributions.

To make the derivation of rate constants simple I start with the postulate that the activation process follows a "least motion" or "adiabatic" path. Since the Eyring transition state theory has a thermodynamic basis, the "adiabatic" model must be consistent with a model that is path-independent, that places no restrictions on how the several transition states are reached. It will turn out, therefore, that the "adiabatic" postulate is not necessary. In esterification, for example, the "adiabatic" postulate is that the conformation of the R_1R_2CH group of the ester $R_1R_2CHCOOCH_3$ does not change during the activation step. An essential assumption is that the several reactant conformers interconvert rapidly and remain in equilibrium. The transition-state conformers need not interconvert but are reached by independent paths.

Equations 1–5 define the preliminaries. Equation 1 is a generalization of the Winstein–Holness equation. Each f_i is the mole fraction of the ith conformer of reactant as defined by the Bolzmann expression, eq 2 and 3. The individual rate constants k_i' are given by the transition-state expressions, eq 4 and 5. The Ri designate reactants and the Ti transition states.

$$k = k_1'f_1 + k_2'f_2 + \ldots \quad (1)$$

$$D = 1 + \exp[-(\Delta G_{R2} - \Delta G_{R1})/RT] + \exp[-(\Delta G_{R3} - \Delta G_{R1})/RT] + \ldots \quad (2)$$

$$f_i = (1/D)\exp[-(\Delta G_{Ri} - \Delta G_{R1})/RT] = (1/D)\exp[(S_{Ri} - S_{R1})/R]\exp[-(\Delta H_{Ri} - \Delta H_{R1})/RT] \quad (3)$$

$$k_i' = a\exp[(S_{Ti} - S_{Ri})/R]\exp[-(\Delta H_{Ti} - \Delta H_{Ri})/RT] \quad (4)$$

$$a = kT/h \quad (5)$$

It should be noted that the derivations make use of three different estimates of rate constants, all based on the free energies of formation of the several transition states. The k_i are referenced to the free energy of formation of some specific reactant conformer R1 (the global minimum, for example). The k_i' are each referenced to the free energy of formation of the corresponding Ri (the "adiabatic" estimate). The k_i'' are referenced to the average free energy of the population of reactant conformers.

It is convenient but not essential to choose the lowest energy conformer as R1; ΔG_{R1} is its free energy of formation. Likewise ΔG_{T1} is the free energy of formation of the corresponding transition state. Even if R1 is the conformer of lowest energy, the corresponding T1 need not also be the transition state of lowest energy. The entropy values are entropies of formation of the individual components and specifically exclude entropy of mixing, which will be introduced separately. The $1/D$ term must be calculated from R1.

Equation 6 defines the k_i values and eq 7 follows by combining eq 3 and 4. The overall rate constant k is given

$$k_i = a\exp[(S_{Ti} - S_{R1})/R]\exp[-(\Delta H_{Ti} - \Delta H_{R1})/RT] \quad (6)$$

$$f_ik_i' = k_i/D \quad (7)$$

$$k = (1/D)(k_1 + k_2 + \ldots) \quad (8)$$

by eq 8 as $1/D$ times the sum of the rate constants k_i for each channel and referenced to ΔG_{R1}. Equation 8 is useful for carrying out the specified averaging.

Equation 8 is in accord with the Curtin principle; the product distribution, given by k_i/k, depends only on the relative energy level of the ith transition state, not on the energy levels of the reactant states. However, the presence of the $(1/D)$ term makes the overall rate constant k dependent on the energy levels of reactant states as well as of transition states.

It is a requirement of eq 8 that the reactant conformers are in thermodynamic (rapid) equilibrium and that the enthalpy of activation for the reaction is sufficiently large compared to the energy spacing of the significant conformers. Otherwise the system must be treated as a series of parallel reactions.

I next show that eq 8 may be derived from thermodynamic arguments. The free energy of activation is to be referenced to the average free energy of the population of reactant conformers. The average value for the enthalpy of formation of the set of reactant conformers may be expressed as eq 9 or as the equivalent eq 10 since the sum of the $f_i = 1$ and hence $f_1 = 1 - f_2 - f_3 - \ldots$. The average entropy is defined in terms of partial molar entropies as shown in eq 11–13. The partial molar entropy of Ri is equal to the entropy of formation of Ri plus an entropy of mixing term, eq 12.[41]

$$\Delta H_{av} = f_1\Delta H_{R1} + f_2\Delta H_{R2} + \ldots \quad (9)$$

$$\Delta H_{av} - \Delta H_{R1} = f_2(\Delta H_{R2} - \Delta H_{R1}) + f_3(\Delta H_{R3} - \Delta H_{R1}) + \ldots \quad (10)$$

$$S_{av} = f_1\bar{S}_{R1} + f_2\bar{S}_{R2} + \ldots \quad (11)$$

$$\bar{S}_{Ri} = S_{Ri} - R\ln f_i \quad (12)$$

Substitution of eq 12 into eq 11 and combining terms gives eq 13. Equation 14 expands $\ln f_i$ and eq 15 defines a hypothetical average entropy in terms of nRi as pure (unmixed) species. Equation 16 is obtained from eq 13 by substituting values from eq 14, and eq 17 follows by substituting values from eq 10 and 15. Equation 18 is derived from eq 17 by converting to exponential form. Hence D may be expressed either in reference to the ΔG_{R1} or in reference to ΔG_{av}. An even greater interchangeability is implicit in eq 2 and 3 since the energies may be referenced to any desired standard state.

$$S_{av} = (f_1S_{R1} + f_2S_{R2} + \ldots) - R(f_1\ln f_1 + f_2\ln f_2 + \ldots) \quad (13)$$

$$\ln f_i = \ln(1/D) + (S_{Ri} - S_{R1})/R - (\Delta H_{Ri} - \Delta H_{R1})/RT \quad (14)$$

$$S_{av}' = f_1S_{R1} + f_2S_{R2} + \ldots = S_{R1} + f_2(S_{R2} - S_{R1}) + \ldots \quad (15)$$

$$S_{av} = S_{av}' - R\ln(1/D)[f_1 + f_2 + \ldots] - f_2(S_{R2} - S_{R1}) - \ldots + f_2(\Delta H_{R2} - \Delta H_{R1})/T + \ldots \quad (16)$$

$$(S_{av} - S_{R1})/R = -\ln(1/D) + (\Delta H_{av} - \Delta H_{R1})/RT \quad (17)$$

$$D = \exp[(S_{av} - S_{R1})/R]\exp[-(\Delta H_{av} - \Delta H_{R1})/RT] \quad (18)$$

Equations 19 and 20 express the rate constants referenced to the average free energy of the reactants, and eq 21, which follows by multiplying the terms of eq 19 by the terms of eq 18, simplifies to eq 8. Since all measurements are either from the conformer of lowest energy or from the average enthalpy and entropy of the system, there are

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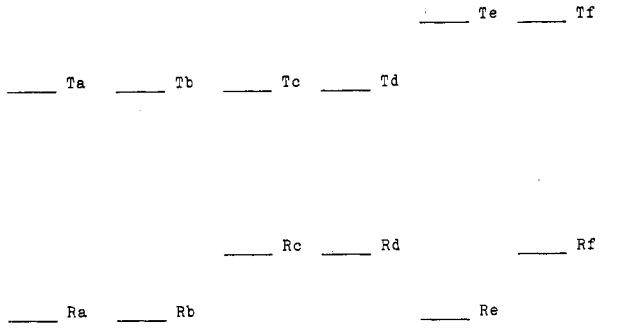
Scheme I



actually no restrictions as to how the reacting conformers get to the several transition states.

$$k = a(\exp[(S_{T1} - S_{av})/R] \exp[-(\Delta H_{T1} - \Delta H_{av})/RT] + ...) \quad (19)$$

$$k = a(k_1'' + k_2'' + k_3'' + ...) \quad (20)$$

$$D \cdot k = a(\exp[(S_{T1} - S_{av})/R] \exp[-(\Delta H_{T1} - \Delta H_{av})/RT] \exp[(S_{av} - S_{R1})/R] \exp[-(\Delta H_{av} - \Delta H_{R1})/RT] + ...) \quad (21)$$

To illustrate the consequences of the derivation, Scheme I shows several hypothetical reactant–transition state pairs. In Table I are shown the separate components of k, the k_i/f_1 values of eq 1; their sum k is the same k given by eq 8. Example HO gives the rate constant based on a single lowest energy conformer of reactant and a single lowest energy conformer of the transition state. (Other conformers are of high enough energy that they may be neglected.) Example H1 shows that the rate constant is unchanged for two (or any number of) entirely equivalent reaction paths. Example H2 shows that extra channels increase the rate constant, while example H3 shows that the presence of nonproductive reactant conformers decreases the rate constant. In all cases the HO rate constant is the reference for comparisons.

Table I. Dependence of the Overall Rate Constant on Conformer Energies[a]

conformers	ΔG_{Ri}	ΔG_{Ti}	f_i	$10^6 f_i k_i'$	$10^6 k$
HO Ra.Ta	0	8	1.0	1.37	1.37
H1 Ra.Ta	0	8	0.5	0.685	
Rb.Tb	0	8	0.5	0.685	1.37
H2 Ra.Ta	0	8	0.936	1.28	
Rc.Tc	2	8	0.032	1.28	
Rd.Td	2	8	0.032	1.28	3.83
H3 Ra.Ta	0	8	0.492	0.67	
Re.Te	0	10	0.492	0.02	
Rf.Tf	2	10	0.017	0.02	0.72

[a] Hypothetical data. For each example the value of k based on the global minima is 1.37×10^{-6}.

In applying eq 8 to esterification reactions the corrections to log k_{calc} ranged from roughly –0.25 to +0.25 where k_{calc} is based on just the global minima.[29] Although the correction is often unnecessary, the standard deviation for the ester study was 0.24 and omitting the correction would needlessly bias the results.

1,3-Dimethyl-3-acyltriazenes: Synthesis and Chemistry of a Novel Class of Biological Methylating Agents†

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The synthesis and hydrolytic decomposition of 1,3-dimethyl-3-(diethoxyphosphinyl)triazene (DMP), 1,3-dimethyl-3-carboethoxytriazene (DMC), 1,3-dimethyl-3-acetyltriazene (DMA), and 1,3-dimethyl-3-(*N*-methylcarbamoyl)triazene (DMM) are described. The kinetics of hydrolysis of DMP and DMC were investigated in aqueous buffers as a function of pH. DMP was found to be subject to acid catalysis up to pH 4.5 but then followed uncatalyzed kinetics up to pH 11.5. DMC, on the other hand, was catalyzed by acid at pH <4.5 and base catalyzed at pH >9.5. It exhibited uncatalyzed kinetics in the intervening pH region. DMA and DMM also appear to follow uncatalyzed kinetics in the vicinity of neutral pH. The order of reactivity of the four triazenes at pH 7.5 was found to be DMP > DMC > DMA > DMM. The mechanism of the hydrolytic decomposition in the uncatalyzed region is seen as a direct dissociation of the acyltriazenes to the methyldiazonium ion and the respective acylamidyl anions. The intermediacy of the methyldiazonium ion during the decomposition of DMC was established by deuterium exchange studies when the decomposition was carried out in deuterium oxide buffers. The four triazenes were tested in a bacterial mutagenesis assay by using the His$^-$ strains of *Salmonella typhimurium*. DMP, DMC, and DMA were found to be directly acting mutagens in strains that require a base substitution to revert to wild type. These results are consistent with the methyldiazonium ion acting as the ultimate mutagen. The mutagenicity of DMC was enhanced by porcine liver esterase, which suggested that this enzyme was capable of hydrolyzing the carboethoxy group to release the highly reactive dimethyltriazene.

The chemistry of 1-aryl-3,3-dialkyltriazenes has been the subject of active investigation for over 30 years.[1] Many members of that class have been shown to have mutagenic,[2] carcinogenic,[3] and antitumor[4] properties. One of these triazenes, 5-(*N*,*N*-dimethyltriazeno)imidazole-4-carboxamide (DTIC) is in use clinically as an agent against metastatic melanoma.[5] A few years ago, we reported on

† This paper is dedicated to Prof. Vladimir Prelog, ETH, Zürich, on the occasion of his 80th birthday.

(1) For a recent review of triazene chemistry and biology, see: Kolar, G. In *Chemical Carcinogens*, 2nd ed.; Searle, C. E., Ed.; ACS Monogr. 184; American Chemical Society: Washington, DC, 1984; pp 869–914.
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