Unimolecular Behavior of Very Large Molecules. 1. Theoretical Preliminaries

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Abstract: We wish to understand what kind of unimolecular theory should be applied to very large molecules, in the size range of enzyme-substrate complexes. As a preliminary to a trajectory test of the RRKM theory, we have studied the limiting behavior of RRKM rate constants when the number of atoms increases. Rates of chain breaking approach zero for bonds near the center of chains, but remain finite and nonzero for end-atom detachment, ring opening at single bonds, and a selection of concerted ring openings involving two bond scissions. These results are remarkably insensitive to the dimensionality and sophistication of the molecular models employed.

Our long-range interest in this series of problems stems from curiosity about the unimolecular behavior of enzyme–substrate complexes. We intend to make a trajectory study simulating the reactions of very large molecules. But a foreground problem interposes itself, and we deal with it here. The conventional RRKM model[1] of these processes, implying rapid intramolecular redistribution of energy, has been applied to specific cases of molecules of modest complexity on the biological or polymeric scale. No one knows what, if any, limits its predictions approach as molecular size becomes indefinitely great. Does it say that rates will approach zero, infinity, or a finite value? There is little point in testing the RRKM model with trajectories if conditions are such that its predictions are clearly unreasonable. Answering this question seems to us a sensible first step toward finding out what kind of theoretical vocabulary is required in a discussion of the efficacy of biological catalysts and the rates of other reactions of large molecules.

Our tactics are to construct a series of artificial molecular models for which RRKM analysis can be carried out as a function of the number of subunits present. These are then examined for asymptotic behavior. We wish to learn whether there is a trend in the conclusions as the complexity and realism of the various models increases. Our eventual dynamical model for simulation will be chosen from among them.

Consider the simple rate constant expression

$$k = \bar{\nu}[(E - E_0)/E]^{s-1} \tag{1}$$

$$\bar{\nu} = \left(\prod_{i=1}^{s} \nu_i{}^*\right)\left(\prod_{i=1}^{s-1} \nu_i{}^+\right)^{-1} \tag{2}$$

which is the classical limit of RRKM theory. The threshold energy for the reaction is E_0, the energy is E, there is a set of s effective classical oscillators having frequencies $\nu_i{}^*$ in the molecule, and the critical configuration has $s - 1$ effective modes with frequencies $\nu_i{}^+$. (The phrases "activation energy" and "activated complex" may be substituted for "threshold energy" and "critical configuration" without intolerable imprecision, in this work.) As s becomes large the average value of energy pool E does also; on the other hand, in a molecule with a large skeleton there will also appear some very low vibration frequencies. Thus it is not immediately clear which term in (1) will dominate.

We deal first with the energy term. The average vibrational energy will be sRT. Express it in terms of s, also E_0 as vRT, v being constant at around 10–100, a bond property.

$$[(E - E_0)/E]^{s-1} = (1 - v/s)^{s-1} = 1 - (s - 1)v/s + (s - 1)(s - 2)v^2/2!s^2 + \ldots \tag{3}$$

The series converges since $s > v$ or else the reaction is energetically infeasible. When $s \gg v$, the series becomes that for $\exp(-v)$, a fairly small constant but not zero. This is approached from below, as can be verified by evaluation of the case $s = v + 1$. Evidently continuously increasing the equipartition thermal energy of the molecule, by adding more atoms, leads to a stable limit. Its magnitude will be influenced by quantum-statistical effects; the important point here is that the rate constant neither vanishes nor blows up with s. The problem then devolves upon the $\bar{\nu}$.

An Illustrative Simple Model

Since we do not intend to obscure the physical significance of each model employed with cumbersome mathematical expressions, most of the details of computation have been left out in this work. However, to show the procedure in a way that does not require computational assistance, we analyze first a one-dimensional Markov chain of identical masses connected by identical bonds. More realistic models follow. For polymeric long chains, the results of this simple model serve as an ample demonstration.

Suppose there are N atoms, and that a piece of the molecule having R atoms is to be detached in a unimolecular process.

$$\bar{\nu} = \left(\prod_{i=1}^{N-1} \nu_i\right)\left(\prod_{i=1}^{R-1} \nu_i\right)^{-1}\left(\prod_{i=1}^{N-R-1} \nu_i\right)^{-1} \tag{4}$$

in which the three products are of the frequencies of the molecule, the detached fragment, and the remaining fragment, respectively. The frequencies arise from the eigenvalues of the Wilson GF matrix;[2] each $\nu = (2\pi)^{-1}\lambda^{1/2}$. Then

$$\bar{\nu} = (2\pi)^{-1}\left(\prod_{i=1}^{N-1} \lambda_i\right)^{1/2}\left(\prod_{i=1}^{R-1} \lambda_i\right)^{-1/2}\left(\prod_{i=1}^{N-R-1} \lambda_i\right)^{-1/2} \tag{5}$$

The F matrix has force constants k along its diagonal, zero elsewhere. The G elements[2] are $2/m$, m being atomic mass, on the diagonal; $-1/m$ for elements whose indices differ by 1; zero elsewhere. The determinant of a matrix is the product of its eigenvalues. Therefore, for this model, (5) can be written

$$\bar{\nu} = (2\pi)^{-1}(2k/m)^{1/2}[D_{N-1}/D_{R-1}D_{N-R-1}]^{1/2} \tag{6}$$

D being a determinant of size indicated by its subscript and having 1 for diagonal elements and $-\frac{1}{2}$ when indices differ by 1, otherwise zero. The individual frequencies need not be known; however, we develop them in the case of later models for interest's sake.

The simple determinants D can be evaluated either by general formula or by repeated expansion of minors

$$D_n = (n + 1)/2^n \tag{7}$$

to be inserted in the ratio of D's in (6). The other factor has the

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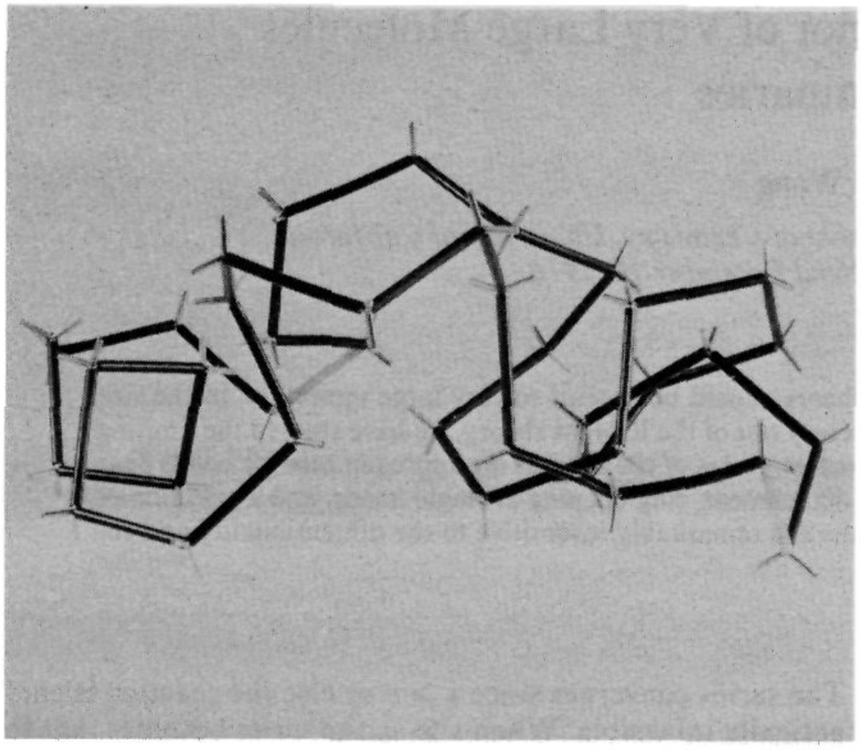

Figure 1. A typical conformation of one of the molecular models.

size of a typical unimolecular rate constant.

$$\bar{\nu} = (2\pi)^{-1}(k/m)^{1/2}[N/R(N-R)]^{1/2} \qquad (8)$$

This shows us that for detachment of an end atom, $R = N - 1$,

$$\bar{\nu} = (2\pi)^{-1}(k/m)^{1/2}[N/(N-1)]^{1/2} \xrightarrow[N\to\infty]{} (2\pi)^{-1}(k/m)^{1/2} \qquad (9)$$

so that the rate constant is of reasonable size no matter how large the molecule. But for breaking a single bond in the middle of the molecule, $R = N/2$ and

$$\bar{\nu} = (2\pi)^{-1}(k/m)^{1/2}(4/N)^{1/2} \xrightarrow[N\to\infty]{} 0 \qquad (10)$$

so the RRKM treatment predicts that this reaction rate can be made as nearly vanishing as desired by adding more atoms.[3]

Note here that there are a large number of nearly equivalent bonds along the chain. Summing over possible decomposition modes from both ends of the molecule toward the middle gives

$$\sum_{R=1}^{N-1} [N/R(N-R)]^{1/2} = 2[N/(N-1)]^{1/2} + 2[N/2(N-2)]^{1/2} + \ldots$$

whose ratio of successive terms approaches 1 for large R. The result is approximately proportional to N, so that on incorporating (10), one finds the combined k for all bonds diverging as $N^{1/2}$ for large N. However, this is offset by the $\exp(-v)$ factors. For example, to break a 21 kcal terminal bond in the presence of N 90 kcal bonds at $RT = 0.6$ kcal

$$N^{1/2} \simeq \exp(150)/\exp(35);\ N \simeq 10^{100}$$

Other estimates also suggest that having strong bonds dissociate in preference to a weak one, by being present in overwhelming numbers, will not be a serious problem for molecules in the size range of our interest.

More Realistic Models

We catalog the nature of the model, what if any additional calculational difficulties are present, and whether the results differ from those described above. In most cases they do not.

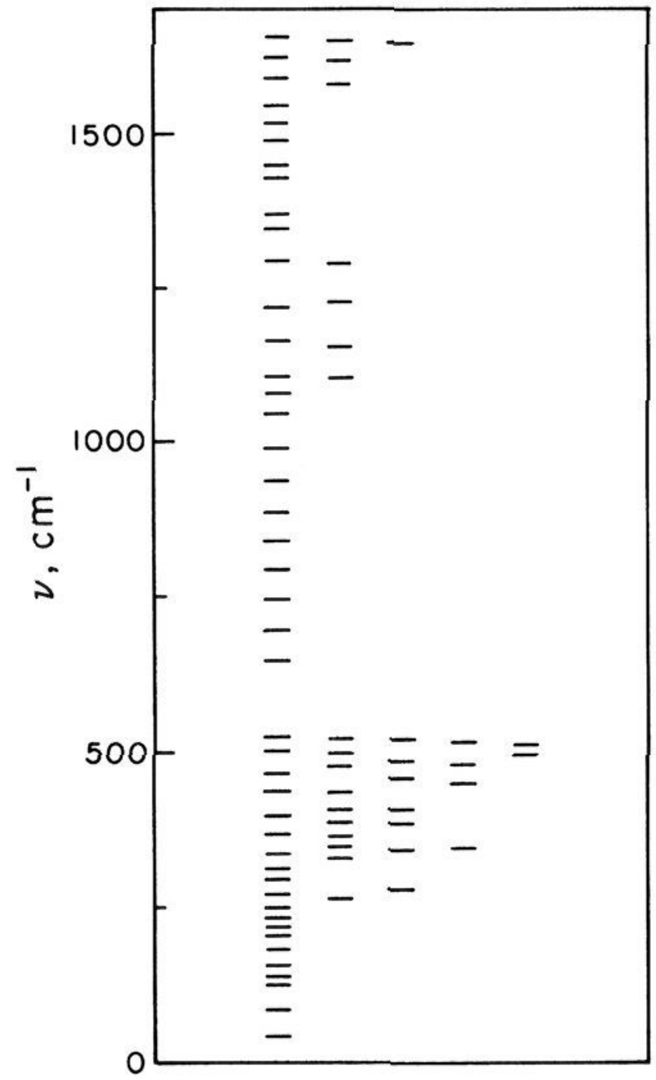

Figure 2. A frequency spectrum for one of the molecular models. There are no degenerate values; horizontal separation is for clarity only.

Cyclic One-Dimensional Case. If the molecule has only stretching motions, but the fixed bond angle is other than 180° ($G_{i,i+1} = \cos\theta/m$ rather than $-1/m$), the simplest ring molecule may be studied. The determinant roots[4] are

$$\lambda_i = 2\{1 + (\cos\theta)[\cos(2\pi i/N)]\};\ i = 1, \ldots, N \qquad (11)$$

for the cyclic case and

$$\lambda_i = 2\{1 - (\cos\theta)[\cos(\pi i/N)]\};\ i = 1, \ldots, (N-1) \qquad (12)$$

for the acyclic case. For a cyclic molecule of this model with an acyclic critical configuration, rate of bond breakage for a selected bond attains constant value for all N.

A Specialized Bending Case. Single bending motion introduced independent of stretching at each atom, with a 180° equilibrium angle and a 135° torsional angle, produces a relatively easily analyzed case. *The first two rows of the determinant*[5] are

$$\begin{matrix} 1 & 0 & -\tfrac{1}{2} & 0 & \ldots \\ 0 & 1 & 0 & (2/9)^{1/2} & \ldots \end{matrix} \qquad (13)$$

with continuation on an alternating-row basis. By minor expansion the following recursion formulas are found; D and E represent two different types of determinants that occur in the expansion.

$$\begin{aligned} D_i &= E_i - [(E_{i-1} - 2D_{i-2}/9)/4] \\ E_i &= D_{i-1} - [2(D_{i-2} - E_{i-2}/4)/9] \end{aligned} \qquad (14)$$

With $D_1 = E_1 = 1$ the evaluation can be carried out to large N very quickly by means of a short computer program. Limits are approached rapidly and the result is the same as for the nonbending cases. The same conclusion applies to other bending angles.

Most General Cases. Full range of interactions are allowed here for the molecule. Both cyclic and acyclic cases were examined to model the ring structures and polymeric long chains correspondently. Beyond this point, experimental computer diagonalization of matrices is required. We used two[6] conventional programs. One is for solution of GF matrix problems and the other is a diagonalization taken from a molecular quantum chemistry program (our matrices are all symmetric). The results from these programs checked one another and, whenever one was available, those from evaluation by formula. Evaluation was carried out up to 76 × 76, which was sufficient[7] for limiting behavior to be discerned. This usually oscillated somewhat for obtuse angles between even and odd members of the series; the amplitude died out sufficiently rapidly. In these calculations the bond angle was always 109° 28′; torsional angles of 0, 45 (α helix), 60, 135, 180, and 210° (twisted β chain) were all examined. Force constants were representative of C–C stretches and C–C–C bends. In the cyclic cases with acyclic critical configurations, two degrees of freedom have to be removed from the critical configuration to be consistent with our constrained mathematics, in which there is still one degree of bending freedom at each joint. A corresponding zero eigenvalue in the analysis is disregarded.

For *chain breaking* the rate behavior for large N is the same as in the simplest one-dimensional case.

For *ring opening at a single bond* the rates increase with N for some time, but might begin to level off at high N. Further test on this is underway.

There were several models studied in which there was *concerted ring opening* at two bonds, intended to be as close as we can come at present to something like an enzyme–substrate complex: (a) two equivalent fragments; (b) R exactly 6; (c) $R = 0.2N$. No new behavior was observed, although there was considerable variation in the oscillatory disturbances and rates of approach to limits, the latter being faster in all cases.

A picture of one of the conformations of our most realistic model is shown in Figure 1. A typical frequency spectrum for such a molecule appears in Figure 2.

Conclusions

The above survey convinces us of the following.

(1) There is no visible a priori reason why the RRKM theory may not be applied to extremely large molecules. It should be the method of choice if its central assumption about rapid internal energy relaxation proves feasible.

(2) There appears to be no trend in the contents of this conclusion as the dimensionality of the mathematical treatment varies. For chain breaking, highly restricted structural frameworks seem to supply valid kinetic models.

(3) Further investigation on the behavior of ring opening, which simulates the biological enzyme–substrate complexes, our long range interest, is underway. The preliminary analysis indicates a meaningful way in interpreting the dynamics of enzyme-catalyzed reaction rates.

(4) It is appropriate and useful to compare the results of calculations like these with trajectory-averaged computational rate constants as a function of N, to test the actual rapidity of intramolecular relaxation. The model initially chosen for this, on account of the simple character of its Hamiltonian mechanics, is the bending chain with tetrahedral equilibrium and 0 or 45° torsional angles. Results will appear in sequel publications.

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References and Notes

(1) RRKM = Rice, Ramsperger, Kassel, Marcus. Sources: P. J. Robinson and K. A. Holbrook, "Unimoleculer Reactions", Wiley, New York, N.Y., 1972; W. Forst, "Theory of Unimolecular Reactions", Academic Press, New York, N.Y., 1973; D. L. Bunker, "Theory of Elementary Gas Reaction Rates", Pergamon Press, Oxford, 1965.

(2) E. B. Wilson, Jr., J. C. Decius, and P. B. Cross, "Molecular Vibrations", McGraw-Hill, New York, N.Y., 1955.

(3) It has been pointed out kindly by our referee that this particular result may also be obtained by treating the molecule as a vibrating string in the one-dimensional Debye model, which is essentially a special case of Markov chain. There will be $N + 1$ frequencies that are harmonics of ν in the molecule, $N/2$ harmonics of 2ν in the fragments. Then

$$\bar{\nu} = \left(\prod_{i=1}^{N+1} i\nu\right)\left(\prod_{i=1}^{N} 2i\nu\right)^{-2} = (N+1)!\nu/2^N[(N/2)!]^2$$

which yields $(N + 1)\nu(2/\pi N)^{1/2}$ by the Stirling approximation.

(4) The formulas can be derived easily from vector analysis of the eigenstates. For example, see T. C. Bradbury, "Theoretical Mechanics", Wiley, New York, N.Y., 1968, p 514, for initial steps.

(5) The determinant is most easily derived by choosing a particular relationship (e.g., $k_r = 3k_\varphi/r^2$) between force constants, and verifying later that the result is insensitive to this choice.

(6) These were supplied by M. Wolfsberg and W. Hehre, respectively, whom we thank.

(7) The calculations were carried out on a minicomputer, the Hewlett-Packard 2108-MX with 16K 32-bit semiconductor memory words. The hard-wired floating-point arithmetic for this word length was used. Time requirements were modest for large N.