Mean Excitation Energies and Energy Deposition Characteristics of Bio-organic Molecules

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Received: September 17, 2009; Revised Manuscript Received: October 30, 2009

We suggest a method for determination of the mean excitation energies of several biomolecules, such as amino acids, using a Bragg-like sum rule developed for molecular fragments or functional groups. Because the fragment composition of many bio-organic molecules is very similar, we find that many of them, including the amino acids, have similar mean excitation energies (~70 eV, which is interestingly close to the mean excitation energy of the major component of a cell: namely, water). Differences in amino acid mean excitation energies arise from variation of the side chains (−R); addition of $-CH_2-$ groups decreases the mean excitation energy.

Introduction

Although the bulk of biological damage resulting from exposure to radiation comes from either single (SSB) or double (DSB) strand breaks in DNA, there is also significant damage from fragmentation of protein. Relatively little damage is produced by direct hits of ions or photons on DNA or protein. Rather, because it is ubiquitous in the cell, most damage arises from decay products of the interaction of radiation with water: from δ (or secondary) electrons which can interact either directly with a biomolecule or indirectly via O• and OH• free radicals produced from initial interaction of the electrons with water, which subsequently fragments. For massive ionizing radiation such as protons and alphas, this is almost entirely the case, whereas for photons, there is a larger possibility of exciting a molecule somewhat larger than water, or an excitation localized on a fragment of a molecule, causing electronic excitation that is followed by fragmentation or decomposition into radicals and electrons. For incident electrons, the process is similar, but here, the electron can be captured into an excited state of the molecule, which fragments into radicals and electrons. Understanding the interaction of radiation, both massive and mass-less particles, with biological targets becomes ever more important as we seek to protect healthy cells from radiation damage and to target therapeutic radiation selectively on pathologic cells.

The problem extends over many orders of magnitude in complexity, time scale, and size as the effects of the interaction of radiation with matter become more complicated. For example, the time scales for bioradiological processes begin with attoseconds (the physical stage, vide infra) and continue through tens of years (e.g., the Nagasaki studies[1,2]).

Describing and understanding the effects of radiological action on biological systems is thus exceedingly complicated because one must describe long chains of sequential and parallel chemical and physical events as well as possible nonlinearities between initial radiogenic molecular changes and final biological effects.[3−5] However, in all cases, the understanding and description of radiological action on biosystems begins with determination of the energy deposited. Massive particles, as opposed to photons, deposit energy in a molecule by energy transfer to either the electrons (the dominant mechanism) or the nuclei of the molecule. The process typically converts projectile kinetic energy to electronic excitation of the target molecule, followed by ionization, decay, emission of secondary radiation, or fragmentation. The energy deposition depends on the electronic structure of the target system and its propensity to absorb energy from a swift projectile. The material constant of the target that quantifies energy absorption is the mean excitation energy. The mean excitation energy of a target is thus a parameter that must be known before theoretical predictions can be made or experiments can be planned, regardless of the theory or model used.

In this study, we are concerned with the basic physics of the very first steps in the process; namely, with the initial interaction and energy transfer from a projectile ion to a bio-organic molecule.

To study the energy transfer consequences of swift ions impinging on representative bio-organic molecules, such as the amino acids and small peptides, we employ Bethe−Born theory and a Bragg-like rule.

Simple Stopping Theory. Energy transfer to a molecule by a fast ion is frequently described in terms of the energy loss, or stopping power, of the target molecule.[6−8] [In the biologically related literature, the stopping power is often referred to as linear energy transfer, or LET, a misnomer because the process is not linear.] To avoid scatterer density differences, one frequently considers the stopping cross section $S(v)$:

$$-\frac{dE}{dx} = nS(v) \tag{1}$$

where n is the number density of the scatterers, and v is the projectile velocity. The cross section is further written in terms of the stopping number, $L(v)$ as

$$S(v) = \frac{4\pi e^4 Z_1^2 Z_2}{mv^2} L(v) \tag{2}$$

Here, Z_1 and Z_2 are the projectile charge and target electron numbers, respectively. The simplest version of stopping theory, which we employ here, is valid for conditions under which the projectile velocity is much larger than that of the target electrons

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10.1021/jp908998s
Published on Web 12/14/2009

and leads to the Bethe−Born[6−9] form of the stopping number, which can be written as

$$L(v) = \ln \frac{2mv^2}{I_0} - \frac{C(v)}{Z_2} \quad (3)$$

The first term on the right-hand side of eq 3 is dominant at high projectile velocities. The second is referred to as the shell corrections and is present to compensate for cases in which the projectile velocity is not much greater than that of the target electrons. At large projectile velocity, C/Z_2 consequently approaches zero. The quantity I_0 is known as the mean excitation energy of the target and is the target material constant for the problem. The mean excitation energy is defined as the first energy-weighted moment of the dipole oscillator strength distribution (DOSD) of the target:

$$\ln I_0 = \frac{\sum_i f_{0i} \ln E_{0i}}{\sum_i f_{0i}} \quad (4)$$

Here, $\{E_{0i}\}$ is the set of electronic excitation energies for the target, and $\{f_{0i}\}$ is the set of the corresponding dipole oscillator strengths. As Inokuti pointed out,[10] "The mean excitation energy, I_0, is the sole nontrivial property of matter appearing in Bethe's expression for the stopping power for a charged particle at high speed. When the dipole oscillator-strength spectrum, df/dE, is fully known as a function of excitation energy, E, the I_0 value may be evaluated from $\ln I_0 = (\int \ln(E\,(df/dE))\,dE)/(\int (df/dE)\,dE)$." The mean excitation energy measures the difficulty with which a target molecule can absorb energy from a massive projectile. Large mean excitation energies correspond to larger difficulty for the absorption of energy and, thus, lead to lower stopping power.

We thus concentrate on the mean excitation energies of some small bio-organic molecules as descriptors of the ease by which they absorb energy, using the amino acids as examples.

The Bragg Rule. Due to the difficulty of quantum molecular calculation of the stopping cross section of large molecules,[11] many calculations have been based on the premise that the cross section for an aggregate system can be determined from a sum of the atomic stopping cross sections ($S_i(v)$) weighted by the number of atoms of each type (n_i) in the target:

$$S(v)^{\text{molecule}} = \sum_{i=\text{atom types}} n_i S_i(v) \quad (5)$$

Such a notion, that the molecular stopping cross section is the simple sum of the cross sections of the atomic constituents, is known as the Bragg Rule.[12] At first glance, it is apparent that the Bragg Rule, at least as stated above, cannot be particularly accurate when representing a molecule as an aggregate of atoms because it neglects chemical binding effects. However, guided by chemistry, one might formulate a Bragg-like rule for molecular fragments—or other aggregates—that includes terms for bonding and thus recovers the effects of chemical bonding within each fragment. We implemented this scheme for small molecules in a cores and bonds approach[13] in which the mean excitation energies corresponding to specific bonds and atomic cores were calculated and used to determine molecular stopping cross sections (vide infra). Others have implemented related approaches.[14]

Because the main contribution to the stopping number is simply related to the mean excitation energy (eq 3), it is also desirable to write a combination law for fragment mean excitation energies that is consistent with the Bragg Rule. In this case, the mean excitation energy, I_0, would be for a molecule containing N electrons and divided into fragments, each with fragment mean excitation energy I_0^i and associated with ω_i electrons. From the definition of I_0 (eq 4), one obtains[13]

$$\ln I_0 = \frac{1}{N} \sum_{i=\text{fragments}} \omega_i \ln I_0^i \quad (6)$$

where $\sum_i \omega_i = N$, the number of electrons in the molecule.

This is the formulation that we will use to calculate the mean excitation energies for some bio-organic molecules of interest. Similar schemes for addition of fragment components for molecular polarizabilities and heats of formation have also recently been implemented.[15]

The Calculational Scheme and Results. In the scheme proposed here, the electron structure of a molecule is divided into core and bond subsets, which are treated separately. Each subset is associated with a mean excitation energy, and these are combined as in eq 6. After treating the core electrons, the valence electrons, including lone pairs, are divided among the remaining bonds, and the bond mean excitation energies are determined according to eq 6. Thus, to obtain bond mean excitation energies, a mean excitation energy of the parent molecule and of the core electrons must be available. For example, to obtain the O−H bond mean excitation energy from that of water, there would be two O core electrons and eight valence electrons. Thus, there would be four valence electrons associated with each of the two O−H bonds. With a theoretical mean excitation energy for the water molecule and a theoretical core mean excitation energy, the bond mean excitation energy can then be determined.

To extract the bond and fragment mean excitation energies necessary to characterize many bio-organic molecules, a set of model compounds and their associated mean excitation energies must be available. Because molecular mean excitation energies, either theoretical or experimental, show considerable variation, we have calculated all of the molecular mean excitation energies directly using the same method for the sake of consistency. Geometry optimization calculations were carried out on the parent compounds using density functional theory (DFT), with the B3LYP functional[16] and using the aug-cc-pVTZ basis sets.[17]

Once the minimum energy molecular geometries were established, all vertical singlet excitation energies and associated electronic transition dipole moments were calculated from the linear response or polarization propagator[18] at the level of time-dependent density functional theory (TDDFT)[19] with the B3LYP functional and the aug-cc-pCVTZ-CTOCD-uc basis set.[17,20,21] In a recent benchmark study[22] of several DFT functionals for the calculation of vertical excitation energies in typical organic chromophores, B3LYP showed the best performance. All calculations were carried out with the TURBOMOLE program.[23,24] Because the calculations are carried out using a finite basis set, we obtained a finite number of excitations equal to the number of one-electron excitations allowed by the basis. As a result, we approximate the continuum with a finite number of discrete excitations (pseudostates) placed such that they represent the continuum. We have found that this discretization of the continuum works well when sums over the entire excitation spectrum are taken, but no significance attaches to the individual pseudostates.[25,26] The DOSD sum rules and mean excitation energies in eq 4 are then obtained by explicit "manual" summation of the oscillator strengths to all bound states and to the discrete continuum pseudostates.

Although TDDFT is hardly on the cutting edge of quantum chemical calculations, two points should be borne in mind. First,

TABLE 1: Calculated Mean Excitation Energies for Parent Compounds

molecule	I_0 (eV)	molecule	I_0 (eV)
CH_4	43.3	CO_2	90.0
C_2H_6	47.0	NH_3	54.7
C_2H_4	51.6	CH_3NH_2	53.5
C_6H_6	59.1	CH_2NH	60.0
H_2O	72.2	H_2S	128.4
CH_3OH	62.4	CH_3SH	97.3
CH_2O	71.4		

TABLE 2: Parameters for Cores, Bonds, and Fragments for Use in Constructing Amino Acid Mean Excitation Energies

atomic cores	mean excitation energy (eV)	ω
Cores		
C_{core} ($1s^2$)	451.34	2
N_{core} ($1s^2$)	590.00	2
O_{core} ($1s^2$)	729.41	2
S_{core} ($1s^22s^22p^6$)	518.75	10
Bonds		
C−H	24.10	2
C−C	28.05	2
C═C	27.05	4
O−H	40.50	4
C−O	43.57	4
C═O	43.35	8
N−H	30.18	8/3
C−N	33.76	8/3
C−S	24.24	4
C═N	33.29	16/3
S−H	22.42	4
Fragments		
$-CH_2-$	64.00	6
$-CH_3$	50.13	8
−phenyl ($-C_6H_5$)	53.06	40
−cyclohexyl ($-C_6H_{11}$)	53.85	46
−COOH	88.60	22
$-NH_2$	67.90	22/3
−OH	106.16	6
−CHO	83.38	14
−NHC(═O)−	89.06	58/3
Amino Acid Common Fragment		
A: $-CH(NH_2)COOH$	75.32	38

the fragment Bragg rule scheme proposed here is itself an approximation, and it would not be cost-effective to employ quantum chemical methods of considerable higher accuracy than the cores and bonds scheme. Second, and perhaps more limiting, is that calculation of the mean excitation energies of the parent compounds requires that the entire excitation spectrum be calculated, which would be impossible using any correlated wave function method.

The calculated mean excitation energies of the parent molecules reported here are given in Table 1. Core mean excitation energies were obtained from previous atomic calculations.[27]

The fragment mean excitation energies were obtained individually by application of eq 6 and the core and bond data in Table 2 together with calculated molecular mean excitation energies from the appropriate parent compounds in Table 1.

In some cases, eq 6 may be applied in two ways. For example, the mean excitation energy of the methyl group ($-CH_3$) can be obtained either by subtracting a C−H bond from the calculated mean excitation energy of methane or by combining three C−H bonds and a carbon atom core according to eq 6. The two schemes give the same mean excitation energies of 50.13 eV. Similarly, the mean excitation energy of the C═O bond can be obtained as derived either from CO_2 or from H_2CO. These two pathways lead to C═O bond mean excitation energies of 43.60 and 43.35 eV, respectively. Internal consistency can also be checked in a larger system, such as cyclohexane. The $-C_6H_{11}$ fragment can be constructed by first constructing the mean excitation energy of C_6H_{12} from contributions from six C−C bonds and six $-CH_2$ fragments ($I_0 = 52.07$ eV) and subtracting the contribution from one C−H bond or by constructing $-C_6H_{11}$ directly from contributions from six C−C bonds, five $-CH_2$ groups, one C−H bond, and one carbon core. Both give a mean excitation energy for the $-C_6H_{11}$ fragment of 53.85 eV.

The other fragment mean excitation energies reported here were obtained as follows:
$-CH_2-$, addition of two C−H bonds and C_{core};
$-C_6H_5$, $I_{benzene}$ minus one C−H bond;
−COOH, addition of C−O, C═O, O−H bonds and C_{core} and twice O_{core};
$-NH_2$, addition of two N−H bonds and N_{core};
−OH, addition of one O−H bond and O_{core};
−CHO, CH_2O minus one C−H bond;
−cyclohexyl, addition of six C−C bonds, and one C−H bond, five CH_2 groups, and C_{core}.

Table 2 presents the cores, bonds, and fragments with the corresponding mean excitation energies used to calculate the total mean excitation energies of the amino acids. We note that the fragment mean excitation energies listed in Table 2 contain the atomic core contributions, but the bond mean excitation energies do not.

The next step is to construct mean excitation energies for the amino acids using eq 6 and the mean excitation energies and weights (ω) from Table 2.

All amino acids can be viewed as a central carbon connected to an amino group, a carboxylic acid group, hydrogen, and a further group, generally denoted as R. The variation in −R is what distinguishes among the amino acids. Thus, one may write an amino acid as $H_2NCHRCOOH$, or A−R, where A is $-CH(NH_2)COOH$. Combining the appropriate groups, one obtains I_0^A which can then be used with the entries of Table 2 to construct mean excitation energies for the amino acids:

$$\ln I_0 = \frac{1}{\omega_R + 38}[38 \ln I_0^A + \omega_R \ln I_0^R] \qquad (7)$$

Few of the mean excitation energies for amino acids have been measured or calculated, which makes comparison difficult. The most comprehensive compilation of these quantities is probably that of Tan et al.[28] These numbers are generated using the dielectric model of Ashley.[29] In this scheme, the proton stopping power is written in terms of the optical energy loss function (OELF), $\mathrm{Im}[-1/\varepsilon(\omega)]$, and $\upsilon(\alpha) = \ln[(1 - \alpha + s)/\alpha]$, where $s = (1 - 2\alpha)^{1/2}$, $\alpha = \hbar\omega/2E'$, $E' = E\, m_e/m_p$, E is the proton kinetic energy, and $\hbar\omega$ is the energy transfer. The stopping power is then written as

$$\frac{dE}{dx} = \frac{1}{\pi a_0 E'} \int_0^{E'} (\hbar\omega)\mathrm{Im}[-1/\varepsilon(\omega)]\upsilon(\alpha)\, d(\hbar\omega) \qquad (8)$$

Comparison of the stopping power determined this way with the Bethe theory of stopping then leads to the mean excitation energy of the target molecule. The problem with this method of determining mean excitation energies for bio-organic targets is that an experimental optical energy loss function is seldom available. Consequently, the OELF is frequently modeled by a Drude function at low energy transfers and photoabsorption cross sections, with an interpolation function in between.[28]

TABLE 3: Calculated Mean Excitation Energies for the 20 Standard Amino Acids

amino acid	R	I (eV)	OELF	other values (eV)	atomic Bragg Rule[33]
alanine	$-CH_3$	67.54	70.4	67.37(T)[26]	71.9
arginine	$-(CH_2)_3NHC(=NH)NH_2$	65.27	67.7		68.6
asparagine	$-CH_2-CO-NH_2$	71.01	73.8		75.5
aspartic acid	$-CH_2-COOH$	73.88	77.0		79.4
cysteine	$-CH_2-SH$	83.98	90.7		93.3
glutamic Acid	$-(CH_2)_2-COOH$	71.27	74.2		76.7
glutamine	$-(CH_2)_2-CO-NH_2$	68.79	71.7	71.9 (E)[34]	73.4
glycine	$-H$	71.15	74.0	71.1 (T)[25]	75.5
isoleucine	$-CHCH_3-CH_2-CH_3$	61.93			66.4
leucine	$-CH_2-CH(CH_3)_2$	61.93	65.1		66.4
lysine	$-(CH_2)_4-NH_2$	62.67	65.8		66.4
methionine	$-(CH_2)_2-SCH_3$	76.33	81.9		84.4
phenylalanine	$-CH_2-Phe$	60.73	69.0		71.1
serine	$-CH_2-OH$	71.29	74.0		76.0
threonine	$-CHOH-CH_3$	68.54			
tyrosine	$-CH_2-Phe-OH$	63.23	71.2		73.1
valine	$-CH(CH_3)_2$	63.29	66.3	67.7 (E)[34]	67.8

Comparison can also be made with the atomic Bragg rule, which occurs when the fragments in eq 6 are simply the constituent atoms. The problem here is to obtain a consistent or standard set of atomic mean excitation energies. Such a set is difficult to obtain because atomic mean excitation energies easily vary by 7−11% among different sets obtained by different methods. For example, the mean ionization potential for oxygen is variously reported to be 115.7[30] and 97.7 eV[31] when extracted from experiment, and 95.0[32] and 93.28 eV[27] when determined from theory. Use of different sets of atomic mean excitation energies can lead to molecular mean excitation energies that differ by more than 10%. For example, the mean excitation energy of cysteine is 92.90 eV when calculated using one set[30] and 75.25 eV when using another.[27]

The mean excitation energies (I_0) for several amino acids, along with the few other values available from experiment (E), theory (T), from calculations using a numerical evaluation of the optical energy loss function (OELF), and from the atomic Bragg Rule as recently reported by Tan et al.[33] are given in Table 3.

Discussion

The fragment mean excitation energies reported here are all calculated at the same level of approximation and with the same basis set, thus producing a consistent set and making comparisons among them meaningful. This is important because the differences among mean excitation energies measured or calculated by various schemes frequently vary more than the average variation among the mean excitation energies of the amino acids. This consistency carries over to other bio-organic mean excitation energies calculated by this scheme, as well, because only one set of fragment mean excitation energies is needed to generate the energy deposition characteristics of the set of bio-organic molecules without size restriction. The OELF scheme,[28] although ideally derived from experiment, requires a difficult-to-obtain optical energy loss function for each molecule and is considerably more problematic to employ.

In the discussion below, the details of molecular connectivity, conformation, and orientation are left out because the calculated mean excitation energy depends on only the various fragments that make up the molecule. Thus, for example, the mean excitation energies of leucine and isoleucine are calculated to be the same because they differ only in connectivity.

It should be noted that use of the atomic Bragg Rule (ABR) reduces the discrimination among structures even further. As mentioned above, the present scheme does not discriminate among target molecules with the same fragments differently connected (i.e., geometrical or position isomers); the atomic Bragg Rule does not even discriminate among functional isomers. Thus, glycine and ethyl nitrite, both being $C_2O_2NH_5$, would be predicted to have the same mean excitation energies. Although the differences in I_0 are expected to be small—for example, the mean excitation energies of Me_2O (59.0 eV) and EtOH (58.3 eV) differ by only a percent—trends can be determined.

Similarly, all of the calculations here are made on the neutral forms of the amino acids, not the zwitterion forms. In an ab initio study of glycine,[25] we found a variation of only a fraction of an electronvolt in the mean excitation energy among various molecular conformations, both neutral and zwitterion, and therefore conclude that use of the neutral form of the molecule will introduce only acceptably small errors into the calculation.

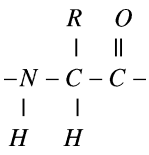
Comparison of these calculated numbers with the little experimental and other theoretical data available (see Table 3) indicate that the numbers produced here should be reliable at the level of a few percent.

In the simple Bethe theory of energy deposition (see eqs 1−3), the mean excitation energy measures the difficulty of depositing energy in a target molecule by a swift ion. Because the stopping power decreases proportionally to ln I_0, the low I_0 amino acids phenylalanine, (iso)leucine, lysine, tyrosine, and valine will be most efficacious in absorbing energy and will have the largest stopping powers. These are the amino acids with the longest carbon chains in −R. On the other hand, amino acids with short carbon chains, such as glycine, alanine, and serine, have higher mean excitation energies and, thus, are less capable of absorbing energy. In many cases, addition of a methylene group to −R decreases the mean excitation energy by 2−3 eV (asparagine/glutamine, aspartic acid/glutamic acid, valine/leucine). This is as expected, because addition of a methylene group will increase the density of states and make energy absorption easier.

The explanation for this behavior is quite clear. As one adds a methylene group to a molecule, one adds eight electrons to the denominator in the prefactor (N in eq 6) in eq 7 and adds the terms 6 ln I_{CH_2} and 2 ln I_{C-C} under the sum. Adding eight to N lowers the first term in the bracket of eq 7 more than the additional logarithm terms increase it, and thus, the mean excitation energy decreases when a methylene is added. This is consistent with the experimental mean excitation energies of

the alkanes,[34] which increase with addition of methyl groups as the dominance of the two contributions is reversed.

Formation of a peptide linkage,



between two amino acids involves formation of an N−C bond and elimination of water. Thus, within the scheme described here, the mean excitation energy for the polypeptide will involve a Bragg-like rule addition of the mean excitation energies of all the constituent amino acids, minus contributions for the N−H bond, the C−O bond, and the −OH group and addition of the contribution for the C−N bond, for each peptide linkage formed.

For example, the mean excitation energy of the glycine dipeptide is calculated to be 71.01 eV, very close to the monomer value. The mean excitation energies of the 3-, 5-, 10-, 50-, and 100-mer glycine polypeptides are 70.95, 70.90, 70.86, 70.82, and 70.15 eV, respectively.

Although the mean excitation energy is not a true intensive property of the amino acids, it is close to it. Thus, because the amino acids have mean excitation energies in the narrow range of 60−75 eV, one would expect that the mean excitation energies of small polypeptides will also be quite close to 70 eV, the average value of those in Table 3. Because the mean excitation energy is nearly intensive, the errors in calculated values would not be expected to increase significantly with protein size. This conclusion is consistent with the OELF result[28] for a protein containing 20 amino acids, which finds $I_0 = 71.4$ eV.

The extension to mixed polypeptides is obvious. Because the mean excitation energies among the amino acids are so similar, it is unrealistic to think that individual amino acids can selectively be fragmented by swift ion radiation.

Finally, although the examples presented here have concentrated on the common amino acids, the scheme presented here is by no means restricted to them. It is applicable to any molecule whose constituent parts are represented in Table 2. Further work will be on the determination of the mean excitation energies of other bonds and fragments of interest in radiation biology.

The advantage of this scheme over others is that it provides a well-defined and consistent method of calculating biomolecular mean excitation energies. Thus, it assures that differences calculated in mean excitation energies of different biomolecular targets are due to differences in structure rather than differences in input parameters.

Acknowledgment. This work was supported by grants from the Danish Center for Scientific Computing, the Carlsberg Foundation and the Danish Natural Science Research Council/ The Danish Councils for Independent Research (SPAS).

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JP908998S