# A Computational Strategy for the Design of Regiospecific Syntheses of Fullerene Derivatives

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The ability to add two or more functionalities to the surface of fullerenes with defined geometry is a key element in expanding the potential applications of fullerene derivatives. This is especially true in biochemical systems, where host–guest binding often depends on the accurate positioning and alignment of complementary surface types. In general there are two ways that regiospecificity can be attained in fullerene synthesis: (1) by exploiting relative reactivities of sites (i.e., the reaction at a single site influences the reactivity of the remaining sites, leading to a specific pattern of modification)[1] or (2) by tying together two reactive groups with a flexible linker, which then directs the addition of the second group upon reaction of the first.[2] In our pursuit of the synthesis of a diamino $C60$ compound as a potential HIV-protease inhibitor,[3] we have developed a computational strategy for evaluating the ability of different linkers to "deliver" the second reactive group to the fullerene surface in a potentially productive manner (i.e., in the desired position). We elaborate upon this strategy here and demonstrate its application to a known linker-assisted regiospecific fullerene modification accomplished by Diederich and co-workers.[2]

The strategy is to find the bond on the C60 that is most likely to be approached by the second reactive group as the linker sweeps through its possible conformations. The computational approach is summarized as follows: (1) Construct a model of the singly reacted species. (2) Generate the entire ensemble of conformers available to the flexible linker that joins the first reactant (now bonded to the C60) and the second reactant. (This is done using the technique of systematic conformational searching where rotatable bonds are driven by some incremental change. (3) Filter this large ensemble for the conformers that place the second reactive equivalent near the surface of the fullerene in a productive manner. (4) For each potential reactive bond on the C60 surface, query whether or not a given conformer positions the second reactive equivalent closely enough and in the correct orientation to react with the bond. (5) Finally, determine the molecular mechanics energy of the conformations that satisfies condition 4, and from these values and the apparent global conformational energy minimum, determine the Boltzmann factor for each of these reactive conformations. By examining the sum of these Boltzmann factors for each potential reactive bond, the probability of finding the second reactive equivalent in a reactive position is assessed and then used to determine the likely position of addition. A similar approach has also been developed by Bruice and co-workers to help understand rates of intramolecular esterifications.[4,5]

We have applied this methodology to analyze a synthesis performed by Diederich and co-workers[2] which utilizes the

(1) Hirsch, A.; Lamparth, I.; Karfunkel, H. R. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 437–438.
(2) Isaacs, L.; Haldimann, R. F.; Diederich, F. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2339–2342.
(3) Friedman, S. H.; DeCamp, D. L.; Sijbesma, R. P.; Srdanov, G.; Wudl, F.; Kenyon, G. L. *J. Am. Chem. Soc.* **1993**, *115*, 6506–6509.
(4) Lightstone, F. C.; Bruice, T. C. *J. Am. Chem. Soc.* **1994**, *116*, 10789–10790.
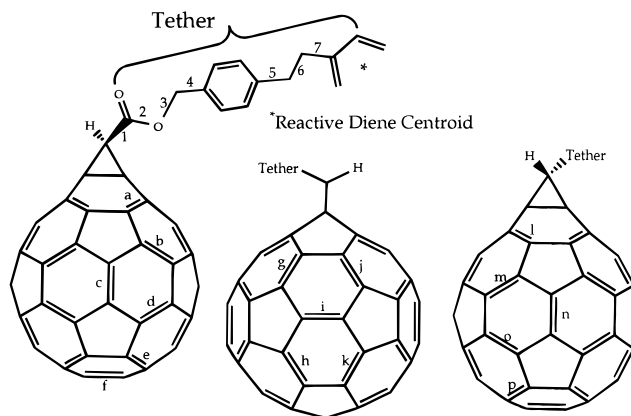(5) Lightstone, F. C.; Bruice, T. C. *J. Am. Chem. Soc.* **1996**, *118*, 2595–2605.



**Figure 1.** Schematic showing tether-linked diene and the 15 unique 6-6 bond targets (a–p) and the seven bonds driven in the search.

approach of tying two reactive equivalents to a flexible linker. They utilized the species shown in Figure 1, which is the product of an initial addition across a 6-6 bond forming a cyclopropyl link. Following this first addition, the diene at the end of the tether adds to a 6-6 bond on the surface in a Diels–Alder fashion. The location of the second group (diene) addition is determined by the conformational nature of the linker. These authors designed the linker they used on the basis of relative energy of the possible products, a reasonable approach that we will comment on below.

We modeled the monoadduct using the program SYBYL.[6,7] A systematic conformational search was initiated by driving each of the seven rotatable bonds with a 30° resolution (a theoretical limit of $3.5 \times 10^7$ conformers). Each of the conformers was analyzed to determine the distance between two centroids. Centroid 1 was at the center of mass of the two reacting diene carbons. Centroid 2 was at the center of mass of the C60 sphere. As each conformation was generated, it was discarded if the centroid 1–centroid 2 distance was greater than 8 Å (i.e., distant from the surface of the fullerene). This filter resulted in a reduction to $\sim 1.2 \times 10^4$ potential reactive conformations.

Each of these remaining conformations was further tested for its ability to position the diene carbons within a reactive distance to possible reactive C60 bonds. This process is simplified because of the known preference in C60 for Diels–Alder reactions to modify at 6-6 bonds. Therefore, only 6-6 bonds were analyzed. For each 6-6 bond, we filtered the potential reactive conformations based on the ability of the conformation to position each of the two reacting diene carbons within a specific distance to the reacting 6-6 bond carbons. In order to assess the effect of this distance on the results of the simulation, we repeated the filtering using a range of distance cutoffs from 4.0 to 3.4 Å. In addition to the distance filter, each conformation was also filtered for the angle of the diene relative to the 6-6 bond. This criteria was set at ≤30°.[8] Because the diene is unsymmetrical, this meant that for each 6-6 bond there were two possible final products related through a 180° rotation of the diene at the time of reaction, designated with subscripts a and b in Table 1.[9] A simplifying factor was the presence of a plane of symmetry in the monoadduct which roughly halved the number of 6-6 bonds necessary to be examined. The final number of filters performed was 31, two for each of the 6-6 bonds except for the one directly opposite to the cyclopropyl

(6) Molecular Modeling System SYBYL, Version 6.2, Tripos Associates, Inc.: St. Louis, MO.
(7) Molecular mechanics energies were generated using the Tripos force field, Gasteiger–Hückel partial charges, and a distance dependent dielectric.
(8) The angle constraint is based on a pseudodihedral formed between the reactive diene carbons, the centroid connecting the two diene reactive carbons, the centroid connecting the two reactive 6-6 bond carbons, and the reactive 6-6 bond carbon. This dihedral is limited to ±30°.

**Table 1.** Summation of Boltzmann Factors for Productive Conformations (satisfying angle and distance cut-offs) at Different Reactive Atom Distance Cutoffs[a]

| 6-6 bond | 4.0 Å | 3.8 Å | 3.6 Å |
|---|---|---|---|
| $b_a$ | $7.2 \times 10^{-2}$ | $3.0 \times 10^{-2}$ | $7.1 \times 10^{-9}$ |
| $b_b$ | $3.9 \times 10^{-5}$ | $9.0 \times 10^{-13}$ | |
| $c_a$ | 1.4 | $3.1 \times 10^{-2}$ | $1.1 \times 10^{-2}$ |
| $d_a$ | $1.2 \times 10^{-2}$ | | |
| $d_b$ | $4.8 \times 10^{-2}$ | | |
| $g_a$ | $9.1 \times 10^{-5}$ | $2.3 \times 10^{-5}$ | |
| $i_a$ | $7.9 \times 10^{-9}$ | $7.7 \times 10^{-9}$ | $7.7 \times 10^{-9}$ |
| $i_b$ | $3.3 \times 10^{-8}$ | $3.3 \times 10^{-8}$ | |
| $j_a$ | $4.9 \times 10^{-7}$ | $4.8 \times 10^{-8}$ | |
| $l_b$ | $8.3 \times 10^{-12}$ | | |
| $m_a$ | $3.0 \times 10^{-8}$ | $3.3 \times 10^{-9}$ | $4.0 \times 10^{-10}$ |
| $m_b$ | $3.6 \times 10^{-8}$ | $3.6 \times 10^{-8}$ | $3.6 \times 10^{-8}$ |

[a] No conformations were observed at the 3.4 Å level. Subscripts a and b for each bond identifier indicate one of two possible orientations of the diene relative to the 6-6 bond.[9] The bonds not listed had no conformations which satisfied the filtering criteria.

group, where symmetry causes the two possible diene adducts to be the same.

The conformations that passed the filter for each bond were noted, and their molecular mechanics energy was converted into a Boltzmann factor using the expression $p = e^{-[(E_c - E_g)/RT]}$, where $E_c$ is the energy of the conformation and $E_g$ is the lowest energy conformation found in the complete search of $3.6 \times 10^7$ conformers. This expression represents a quantity that is proportional to the probability of observing a specific energy state, in this case a potentially reactive conformation. The results of this summation are listed in Table 1.

The aim of this simulation is to find which of the possible reactive 6-6 bonds is most likely to be near the reactive diene in a productive orientation. The $c_a$ isomer is the sole product experimentally observed by Diederich and co-workers.[2] These simulation results show that, for the three limiting cutoff distances, the sole experimentally observed product ($c_a$) is the

(9) The designations of subscripts a and b for each labeled 6-6 bond are to indicate the manner in which the diene adds to it. The a isomer is the one in which the reactive diene carbon that is adjacent to the carbon which is attached to the tether is within the cutoff distance from the carbon in the 6-6 bond which is closest through space to the cyclopropyl base (or to the carbonyl carbon of the tether in cases where the two carbons in the 6-6 bond are equidistant from the cyclopropyl base).

product which has the highest "contact probability" from among the 31 possible products. For the intermediate cutoff value of 3.8 Å, the experimentally unobserved $b_a$ isomer has close to the same Boltzmann summation as the $c_a$ isomer. The ability of this relatively simple analysis to rapidly indicate likely targets of addition suggests that it may be useful in designing other regiospecific fullerene syntheses, especially as greater sophistication of the models used is introduced (i.e., higher resolution searches and inclusion of quantum mechanics to analyze "productive" conformations).

A significant factor that has not been included in the simulation is the intrinsic reactivity of each 6-6 bond. There is evidence that there is considerable variation in subsequent 6-6 bond reactivity following an initial 6-6 bond addition.[10] As other information about intrinsic site reactivity becomes available, either from theory or experiment, it can be included in our computation by scaling the final summed Boltzmann factors. Also, further experimental results can feed back into determining what are optimal filtering distances and angles.

Diederich and co-workers approached the tether design problem by analyzing the theoretical energy of the possible reaction products produced by a given tether. The tether that they chose produced a modeled product (the $c_a$ isomer final reaction product) that was 5 kcal/mol lower in energy than the $b_a$ product (i.e., the product that would be formed by reaction of the bond b), as determined using semiempirical calculations. This is a reasonable approach insofar as the product of the reaction fairly represents the structure and energy of the activated complex, which is not necessarily the case. The methodology we have presented in this paper provides an alternate approach to the solution of the problem of predicting the sites of intramolecular reactivity by analyzing the relative populations of potentially reactive conformations. It is our hope that this approach to the problem of designing regiospecific fullerene syntheses may prove a practical tool as well as a route to understanding and modeling reaction dynamics.

(10) Hirsch, A.; Lamparth, I.; Grosser, T.; Karfunkel, H. R. *J. Am. Chem. Soc.* **1994**, *116*, 9385−9386.