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Conformational Modeling of a New Building Block of Humic Acid: Approaches to the Lowest Energy Conformer

LAWRENCE T. SEIN, JR.,† JAMES M. VARNUM,‡ AND SUSAN A. JANSEN*,†

Department of Chemistry, Temple University, Philadelphia, Pennsylvania 19122, and Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, Pennsylvania 19107

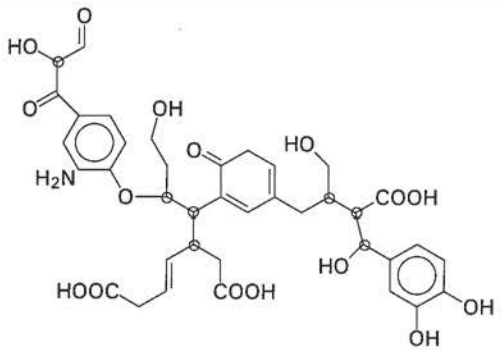
Multiple structural models of humic acid (HA) building blocks have been reported. In this work, the modeling is based on two structural motifs: (i) the Steelink structure and (ii) a new humic acid [TNB] building block, which incorporates more fully the results of experimental data and retro-biosynthetic analyses. Both have significant conformational freedom complicated by their stereochemistry. A molecular modeling approach for the analysis of complex molecules with significant conformational freedom is described as it relates to the newly proposed humic acid building block. A potential energy surface for various conformers of the low-energy stereoisomer has been generated. Included in this discussion is the relationship of the stereochemistry to conformation and secondary structure.

Introduction

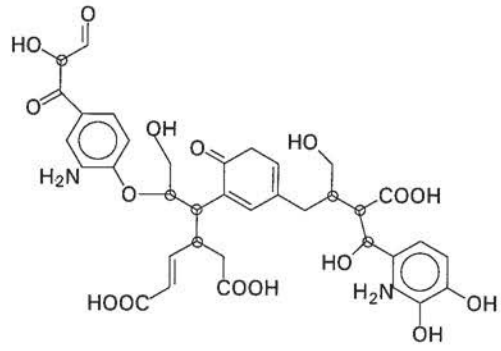
Although humic acid (HA) has been studied extensively for its remarkable environmental, biochemical, and therapeutic properties (*1*–*22*), little extensive modeling on HA has been performed, due in part to the incredible structural diversity in each of the proposed building block (BB) structures (*23, 24*). Until recently, the primary structure of the BB was poorly defined. The most commonly accepted models show the potential for multiple conformational isomers. Some appear so random that they cannot be easily linked to common biological raw materials (*23, 25*). Since humic-like materials are found in living plants (*2, 3, 26*–*28*), it is anticipated that their structure(s) will be well-defined, having resulted from controlled biosynthesis from a limited number of components (*29*) or from abiotic reactions involving biological degradation products. Our HA models possess multiple chiral centers. The first is the Steelink model, and the second is the TNB (Temple–Northeastern–Birmingham) structure as described previously (*27, 29*) (Figure 1).

Molecular modeling of such complex structures as these proposed HA BBs (Figure 1) presents unique problems (*30*). The standard approach is to minimize the energy of a trial geometry. The molecule is then subjected to molecular dynamics (MD) or simulated annealing (*31, 32*) to search conformational space. Resulting conformations are minimized in search of a global minimum. For complex systems, this cycle must be repeated using different starting geometries. This is an inefficient way to search conformational space, especially for complicated structures such as those in Figure 1 (*33*). Searching methods have been developed to address these problems (*30, 32, 34*–*37*). Deterministic methods systematically alter torsion angles (*33*), theoretically allowing a complete search of conformational space (*33, 34*). Stochastic methods (*30, 32, 35*–*39*) (Monte Carlo searches; *40, 41*) generate geometries using (pseudo)random variations in molecular geometry. Stochastic methods can vary internal coordinates, interatomic distances, or torsion angles. Random searching methods allow inversion of chiral centers, which is important when the stereochemical configuration is unknown.

Another peculiarity of conformer searching of HA BBs is that, in contrast to proteins, polypeptides (*42, 43*), and



(a)



(b)

TNB

FIGURE 1. Molecular structure of (a) Steelink and (b) TNB humic acid monomers showing chiral centers as open circles.

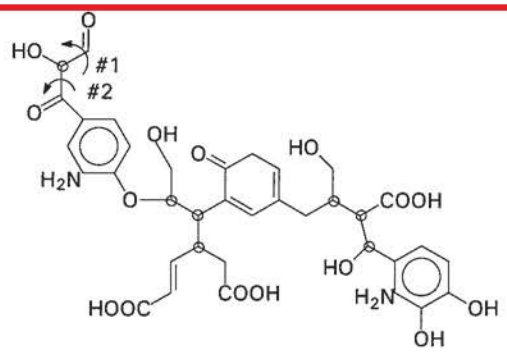


FIGURE 2. Molecular structure of TNB HA monomer showing bond torsions varied. See text for details.

* Corresponding author phone: (215)204-7118, ext 1470; fax: (215)204-1532.
† Temple University.
‡ Thomas Jefferson University.

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