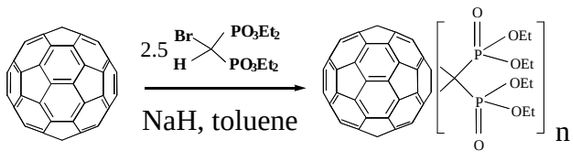
FUNCTIONALIZATION OF C_{60} WITH DIPHOSPHONATE GROUPS: A ROUTE TO BONE-VECTORED FULLERENES

Andrey L. Mirakyan and Lon J. Wilson
Center for Nanoscale Science and Technology and
Department of Chemistry, Rice University,
P.O. Box 1892, MS-60 Houston, Texas 77251-1892,
USA.

Since the discovery of a method in 1990 for the efficient production of macroscopic quantities of fullerenes, potential applications for these materials have been explored intensively. One of the most promising areas of this research now appears to be in the field of medicine.[1] The continued development of such applications will, in general, require functionalization of fullerenes with tissue-targeting moieties to help insure the delivery of any drug to a specific site in the body.

The long-term goal of this work has been to synthesize water-soluble, tissue-vectored derivatives of C_{60} which might be considered as model systems for the design and study of tissue-selective fullerenes, in general. Hydrophilic diphosphonate groups are known to possess high affinity for the bone mineral hydroxyapatite (HAP).[2] Thus, functionalization of C_{60} with diphosphonate groups should lead to bone-vectored, water-soluble fullerene derivatives.

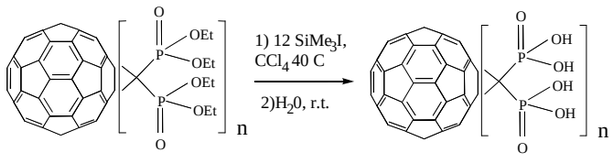
A Bingel-type reaction (Scheme 1) which involves cyclopropanation of a 6,6 double bond in C_{60} with a methylenediphosphonate group was used.[3,4]



Scheme 1.

The monoadduct, five bisadducts *(e, trans-4, trans-3, trans-2, trans-1)* and one trisadduct *(e,e,e)* were isolated using HPLC and flash chromatography. The structures of the different isomers were established using their $^{31}P\{^{1}H\}$ and ^{13}C NMR spectra. In some cases, comparison of the relative polarities of the isomers with the order of elution was also considered.

The monoadduct, the three major isomers of the bisadduct, *trans-2-*, *trans-3-*, and *e-* $C_{60}[C(PO_3Et_2)_2]_2$, and the trisadduct were hydrolyzed to obtain the corresponding diphosphonic acids, as shown in Scheme 2.



Scheme 2.

The polydiphosphonic acids show moderate solubility in polar organic solvents (DMF, DMSO) and also in water. Converting to the sodium or potassium salts leads to a slight increase in water solubility. Biological testing of this compounds are presently underway and available results will be reported .

1. Wilson L. J. *Interface,* 1999, ***8***, *24.*
2. E. Van Beek, M. Houkstra, M. Van de Ruit, C. Lowik, S. Papapoulos *J. of Bone and Mineral Research,* 1994, ***9***, *1875.*
3. F. Cheng, X. Yang, H. Zhu and Y. Song *Tetrahedron Letters* 2000, *41, 3947-3950.*
4. Mirakyan A., Wilson L. J. *J.Chem. Soc. Perk Trans. II.*, submitted for publication.