NMR spectrum (Figure 1B) showed ${}^{13}C_3$ enrichment in all four alkaloids (molar composition **1**:**2**:**3**:**4** = 28:17:41:14%). The incorporation into the four alkaloids, **1**, **2**, **3**, and **4**, calculated from the relative intensities of the singlet and doublet signals due to C-3, was 2, 98, 8, and 97%, respectively. The high efficiency of incorporation of label from cathinone into the noralkaloids explains why cathinone had not hitherto been detected in *Ephedra*.

Scheme I shows the biosynthetic sequence that is now established for the route to the *Ephedra* alkaloids.

Acknowledgment. This work was supported by a grant from the Natural Sciences and Engineering Research Council of Canada. We thank N. Rastrup Andersen, Leo Pharmaceutical Products, for recording the ${}^{13}C$ NMR spectra and N. J. Bollerup, The Geographical Garden, Kolding, Denmark, for a gift of *Ephedra* plants and help with their propagation.

The Electronic Structure of $Sc_3@C_{82}$

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Received October 8, 1992

Soon after the discovery of C_{60} in 1985, researchers found that metal atoms could be trapped not only in C_{60} but in higher fullerenes as well.[1-8] Since the development of the carbon-arc method of fullerene preparation,[9] many of the higher fullerenes have proven to be capable of encapsulating more than one metal atom, as in the recently reported $La_2@C_{80}$,[4] $Y_2@C_{82}$,[6] and $Sc_3@C_{82}$.[8,10] Although a number of metal fullerene species have been reported, the nature of the cluster–fullerene interaction within the cage has received limited attention.[11-13] Work by Manolopoulos and Fowler has shown that a C_{3v} symmetry isomer of $C_{82}{}^{2-}$ is a particularly stable species.[13] Kikuchi and co-workers have shown from NMR results that one isomer of C_{82} does indeed have C_{3v} symmetry.[14] $Sc_3@C_{82}$ has been studied by EPR spectroscopy, and results indicate that the molecule either has C_{3v} symmetry or is fluxional.[8] Although no further conclusions were drawn as to the geometry of this molecule or to the position of the Sc_3 triangle, it seems likely that the C_{82} cage in $Sc_3@C_{82}$ has C_{3v} symmetry and that reasonable placement of the Sc_3 triangle within the carbon cage will enable us to use extended Hückel calculations to examine the electronic structure of the $Sc_3@C_{82}$ molecule. (There is no reason to assume that the C_{82} framework of $Sc_3@C_{82}$ is the same as the empty fullerene.)

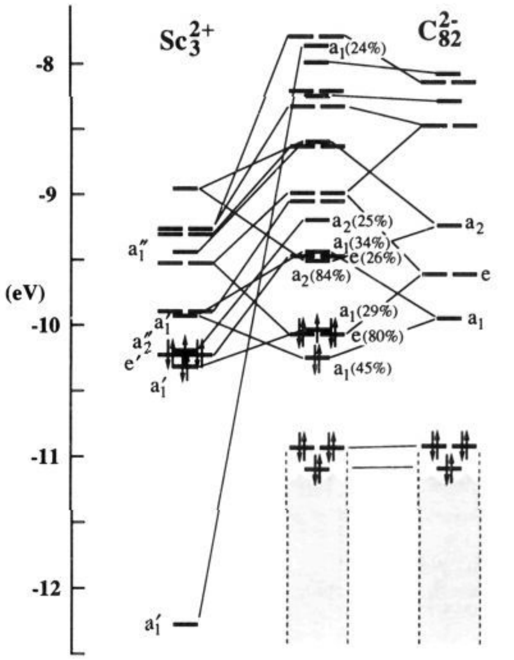

Figure 1. Molecular orbital diagram from an extended Hückel calculation on $Sc_3@C_{82}$ for the proposed C_{3v} geometry (**1**). The shaded area indicates the dense region of occupied orbitals of primarily C_{82} character. C_{82} contributions are indicated in parentheses. Correlation lines indicate the primary orbital parentage from the two fragments, some of which are described in the text. The lowest lying a'_1 orbital of the naked $Sc_3{}^{2+}$ fragment is shown without two electrons in order to make clear the orbital occupancy of the *neutral* Sc_3 cluster, not to indicate the ground state of the dication.

Starting with the C_{3v} symmetry C_{82} connectivity suggested by previous workers,[14,15] we used MM2 calculations with the CAChe system (Computer Aided Chemistry, Tektronix Inc., Beaverton, OR) to obtain a model input geometry of the C_{82} molecule for subsequent extended Hückel calculations. The molecular mechanics parameters were set so that all atoms were sp^2 hybridized. This C_{3v} isomer of C_{82} is built up of 12 pentagons and 31 hexagons, and the bottom of the molecule can be thought of as the carbon framework of the coronene molecule. Placing the Sc_3 trimer ($d(Sc–Sc) = 2.98$ Å) inside the cage with its center 2.5 Å above the center of the coronene unit centers the Sc_3 fragment within reasonable bonding distance of the carbon framework ($d(Sc–C) = 2.15$ Å). **1a** shows a view of $Sc_3@C_{82}$ from the top, with the coronene unit directly below the metal cluster; **1b** is a side view of the molecule showing the vertical positioning of the cluster within the cage.

We obtain energy levels for the naked Sc_3 cluster that are consistent with Knight and co-workers' EPR results for a Sc_3 cluster in a cryogenic matrix,[16] though our energy level scheme is different from either of the possible schemes put forward by those investigators. The lowest occupied orbital of the Sc_3 is mostly an a'_1 bonding combination of Sc 4s orbitals, as suggested by Knight and co-workers. The remaining four closely spaced occupied levels of the Sc_3 triangle are consistent with the low-lying configurations studied by Walch and Bauschlicher for the free Sc_3 and $Sc_3{}^+$ species using ab initio theory.[17] Consistent with

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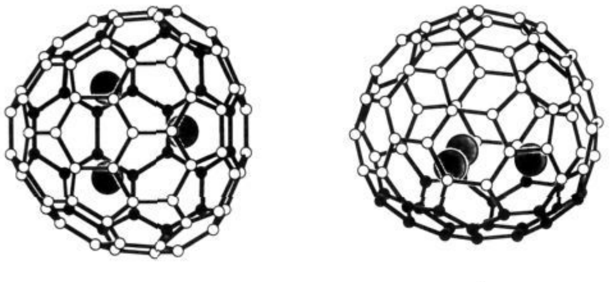

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this ab initio treatment, the a''_2 orbital is the cluster SOMO (singly occupied MO) and the general correspondence with better theory is encouraging. The energy level diagram we calculate for the C_{82} fragment is similar to results obtained by Manolopoulos using the simple Hückel method.[13]

Many of the endohedral fullerene complexes have been interpreted as species with encapsulated ions, $M_x^{n+}@C_m^{n-}$. As a rough approximation $Sc_3@C_{82}$ can be formulated as $Sc_3^{2+}@C_{82}^{2-}$, but this neglects some important mixing between unoccupied C_{82}^{2-} orbitals and the Sc_3^{2+} fragment. Figure 1 shows the percentage of fullerene character in the highest occupied and lowest unoccupied levels for C_{82}^{2-}; the mixing is evident. In contrast, Mulliken population of the occupied C_{82}^{2-} orbitals show that they generally retain greater than 90% fullerene character. A key result of our calculations is that the most bonding orbital for the Sc_3 fragment interacts strongly with several low-lying C_{82} orbitals and is destabilized. Consequently, this orbital is pushed much higher in energy and is unoccupied in the $Sc_3@C_{82}$ molecule. $Co_3(CO)_9S$, $FeCo_2(CO)_9S$, and $Ni_3(CO)_2(C_5H_5)_3$ are particular examples involving trinuclear metal clusters similar to the Sc_3 fragment in $Sc_3@C_{82}$ and are instances in which EPR studies confirm the symmetry and detailed nature of the highest occupied molecular orbital.[18,19] As in this instance, the 4s cluster orbitals are strongly destabilized by interaction with occupied ligand-based orbitals and are pushed well into the unoccupied manifold.[19] C_{82}^{2-} and other fullerenes are unique ligands that may stabilize otherwise unisolable clusters, but it is clear that fullerene cages do not comprise "inert matrices" for the endohedral species which they envelop.

The interaction diagram for $Sc_3@C_{82}$ in Figure 1 shows how the fullerene cage induces significant shuffling in the ordering of the Sc_3 cluster MOs. Four orbitals with varying degrees of Sc_3 character are occupied in the $Sc_3@C_{82}$ molecule, and each of these orbitals is significantly modified from the form that the occupied orbitals take in the free cluster. The SOMO of the naked Sc_3 fragment is of a''_2 symmetry, but it is destabilized after interaction with the cage. The SOMO in the $Sc_3@C_{82}$ molecule is of a_1 symmetry and is largely derived from the 2nd lowest valence orbital of the naked Sc_3 after mixing with the LUMO and other orbitals of the C_{82}^{2-} fragment. Several of the lowest unoccupied molecular orbitals of the C_{82} fragment mix significantly into the four highest occupied orbitals of the endohedral cluster. Accounting of the 337 electrons of $Sc_3@C_{82}$ places a single unpaired electron in the nondegenerate orbital, which is consistent with the EPR results for this molecule.

We should acknowledge that our placement of the Sc_3 cluster within the C_{82} cage is arbitrary with respect to the vertical positioning of the cluster (see **1a**). Calculations with the cluster placed at different 3-fold sites were performed and yield similar results with respect to the overall qualitative interaction between the Sc_3 fragment and the surrounding carbon framework, but the resulting HOMO–LUMO gaps are smaller. The measured shift in the *g*-value (1.9985) indicates that the cluster's unpaired electron resides in a nondegenerate orbital (a_1 or a_2) that is spaced reasonably far in energy from orbitals which can contribute to the ground state via spin–orbit coupling (a_2 or a_1, respectively). We obtain the best agreement with the EPR results with the calculations discussed above. More convincing structural evidence awaits the isolation of $Sc_3@C_{82}$ in greater quantities.

Acknowledgment. We gratefully acknowledge the National Science Foundation for its support through a Presidential Young Investigator Award (Grant DMR-8858151).

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Pulsed-Field Gradient-Enhanced Three-Dimensional NMR Experiment for Correlating $^{13}C\alpha/\beta$, $^{13}C'$, and $^{1}H\alpha$ Chemical Shifts in Uniformly ^{13}C-Labeled Proteins Dissolved in H_2O

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Received November 24, 1992

The development of multinuclear, multidimensional NMR spectroscopy has greatly increased the size limitations of proteins whose structures can be solved by NMR methods.[1-7] The first class of experiments developed consists of those which detect the NH chemical shift during acquisition and hence must be recorded on samples dissolved in H_2O. The second class of experiments, including the HCACO and the HCA(CO)N experiments among others, detects the Hα resonances during acquisition, and spectra are obtained on samples dissolved in D_2O.[1-2] The development of pulsed field gradient technology offers the attractive possibility of recording the latter class of experiments in H_2O, as well, by using these gradients to suppress the undesired water resonance. This has the significant advantage in that all of the spectra necessary for obtaining backbone assignments can be recorded on a single sample, thus eliminating ambiguities with comparing chemical shifts from samples which were prepared under slightly different conditions and which can show significant isotope shifts of the ^{15}N and carbonyl (C′) resonances.[1] In this communication, a pulsed-field gradient experiment is presented for correlating Cβ/α, C′, and Hα chemical shifts. Gradients are used to suppress the intense water signal which would otherwise obscure many of the cross-peaks.

Figure 1 illustrates the pulse sequence that is employed to provide the Cβ/α, C′, Hα correlations. The path of magnetization transfer can be described concisely as

$$H\beta/\alpha \xrightarrow{J_{CH}} C\beta/\alpha(t_1) \xrightarrow{J_{C\alpha C\beta}} C\alpha \xrightarrow{J_{C\alpha C}} C'(t_2) \xrightarrow{J_{C\alpha C}} C\alpha \xrightarrow{J_{CH}} H\alpha(t_3)$$

where the active couplings involved in each magnetization-transfer step are indicated above each arrow. The gradient pulses were positioned in the sequence in order to minimize the water signal and aid in the elimination of artifacts.[8-10] The first gradient pulse,

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