The Valence Isomerization of Cyclooctatetraene to Semibullvalene**

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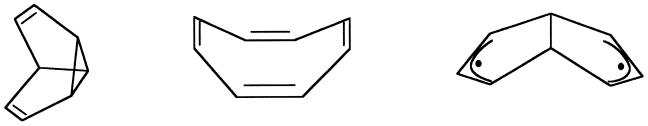
Tricyclo[3.2.1.0^{2,8}]octa-2,6-diene or semibullvalene (SBV; **1**), an isomer of 1,3,5,7-cyclooctatetraene (COT; **2**) was isolated by Zimmerman and Grunewald.[1] At $-140\,^{\circ}C$, it has the lowest energy barrier of any presently known compound capable of undergoing the Cope rearrangement of the double bond system. This barrier to the thermal



1 **2** **3**

isomerization has been determined experimentally to be 5.5 ± 0.1 kcal mol^{-1}.[2] High level theoretical studies of the Cope rearrangement have been recently reported.[3, 4] Martin, Urbanek, and Walsh[5] established that COT should be the principal product of thermal decomposition of SBV. Further, the heat of formation of SBV was estimated to be $\Delta_f H^0 = 73.6 \pm 1.0$ kcal mol^{-1} (298 K), a value close to the experimental value of COT $\Delta_f H^0 = 71.1 \pm 0.3$ kcal mol^{-1} (298 K). The experimental results clearly show that SBV and COT lie close in energy and that COT is involved in two reversible valence isomerization processes: The isomerization at about $100\,^{\circ}C$ produces bicyclo[4.2.0]octa-2,4,7 triene[6] and has been extensively studied.[7, 8] The other isomerization is observed at $300\,^{\circ}C$ and leads to SBV. Martin, Urbanek, and Walsh postulated that the mechanism of the conversion of SBV to COT probably involves the intermediate bicyclo[3.3.0.0]octa-2,6-dien-4,8-diyl diradical **3**, which suggests a stepwise mechanism for the reaction. From a thermochemical estimate,[9] they established a value of $\Delta_f H^0 = 95 \pm 4$ kcal mol^{-1} for this intermediate but, in their conclusions, the authors also stated its formation is not rate determining for the higher temperature COT rearrangement.

The participation of intermediate **3** in the valence isomerization of COT to SBV had been already suggested in an early theoretical study by Iwamura and Morio[10] on the basis of an analysis of the symmetry of the reaction. The transition structure, starting from COT, belongs to the C_2 symmetry group, whereas the product SBV belongs to the C_s symmetry group. The authors concluded that the two structures had to be connected by a structure of C_{2v} symmetry that contained elements of both symmetry groups and thereby postulated the intermediate structure **3**. The limitations in the theory existing at that time prevented a full explanation of the dynamics of these fascinating, interrelated chemical processes, which are of fundamental importance in modern chemistry. In contrast, the introduced concept of bifurcation[11, 12] leads to a logical and consistent explanation of both such chemical processes that are, at first glance, considered to be different.

Herein we report theoretical results supporting the Martin, Urbanek, and Walsh arguments but some corrections were introduced in the construction of the potential energy hypersurface (PES) of the interconversion **1**→**2**. High level quantum-chemical methods were used in our study: the G2 theory for the thermochemistry and Multiconfigurational CASSCF calculations for the equilibrium between SBV and COT. All the calculations were performed with the Gaussian 94 and Gaussian 98 suite of quantum-chemical programs.[13]

To investigate the possibility of a thermodynamical equilibrium between SBV and COT, we carried out G2(MP2) and G2 calculations on the COT isomers involved in the VI process.[14] To our knowledge, these computations are the second example of the application of such methods to a system of the size studied here.[8] The enthalpies of formation for SBV, COT, and **3** are given in Table 1. For SBV and COT, the theoretical results are within the limits of the experimental error, while the calculated enthalpy of formation of the putative intermediate **3** clearly differs from the estimated value. This difference encourages us to search for an alternative reaction pathway. However, our calculated $\Delta_f H^0$ value situates this diradical **3** near to the transition state of the valence isomerization from COT to SBV (heat of formation 114 kcal mol^{-1} [5]).

Table 1. Calculated (G2(MP2) and G2) and experimental heats of formation [kcal mol^{-1}] at 298 K for COT **2**[a], SBV **1**, and the diradical **3**.

	COT **2**		SBV **1**		Diradical **3**	
Method	G2(MP2)	G2	G2(MP2)	G2	G2(MP2)	G2
Atomization	77.2	75.8	77.6	76.1	116.3	115.4
Bond separation	72.0	71.4	72.9	72.2	–	–
Experimental	71.1 ± 0.3[b]		73.6[c]		95.0[d]	

[a] Results from ref. [8]. [b] Value obtained from experimental $\Delta_f H^0_{liq}$ and ΔH^0_{vap} (see refs. [13] and [14] in ref. [8]). [c] Value taken from ref. [5]. [d] Estimated value, taken from ref. [12] in ref. [5].

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It is also important to highlight that this biradical is involved in another valence isomerization of COT: the interconversion to 1,5-dihydropentalene. This process, and the rearrangement of tricyclo[3.3.0.0^{2,6}]octa-3,7-diene to SBV, were also considered in the paper of Martin, Urbanek, and Walsh[5] and will be the subject of a forthcoming paper from us.

The reaction pathways were studied at the CASSCF/6-31G(d) level. With an active space of eight electrons in eight orbitals, the stationary points were characterized by analytical frequency calculations at the same level and the energies were corrected with CASMP2 single-point calculations. Starting from COT, this method allowed us to locate the proposed C_2-symmetric transition state (TS). An intrinsic reaction coordinate (IRC) calculation in the direction of SBV showed that the TS leads to a structure of C_{2v} symmetry which corresponds to the structure proposed by Iwamura and Morio.[10] However, this structure was identical to that for the Cope rearrangement, which was previously found in a detailed investigation of the Cope rearrangement of SBV at several levels of theory (HF, CASSCF, CASPT2N, and DFT (Becke3LYP)).[3, 4] The calculated energetic barrier between COT and SBV, shown in Figure 1, is similar to the estimation of Martin, Urbanek, and Walsh.[5]

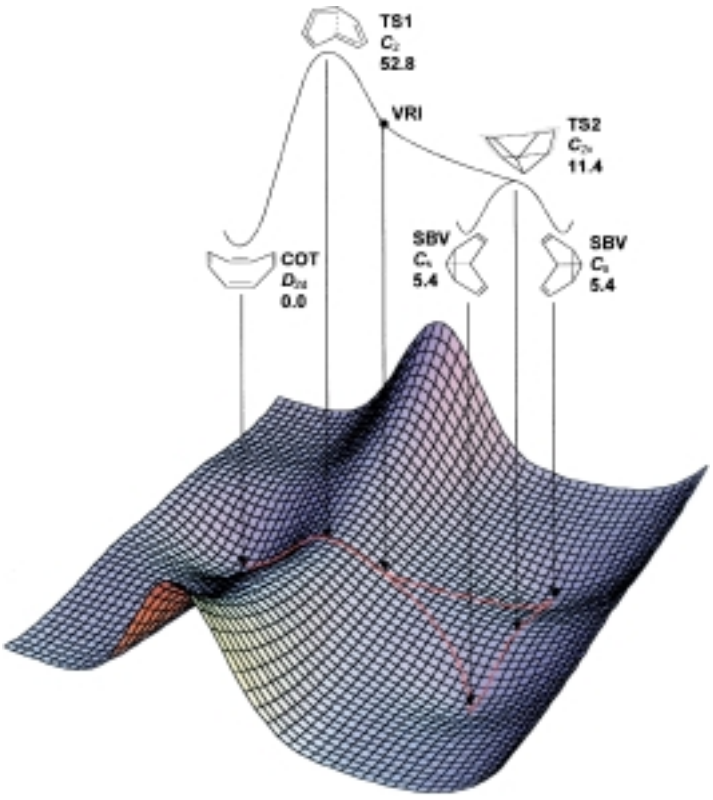

Figure 1. Potential energy hypersurface for the transition from COT to SBV through the transition states TS1 and TS2 and the bifurcation point VRI. The $\Delta_f H^0$ (0 K) values [kcal mol^{-1}] are relative to COT.

Therefore, our IRC calculation shows that the two transition states are connected along the C_2 symmetry coordinate. It can be shown mathematically that along the IRC there must lie a valley–ridge inflection (VRI) point or a bifurcation, a point where a) the energy Hessian projected onto the space orthogonal to the IRC has one eigenvector orthogonal to the curve with its eigenvalue equal to zero, and b) the derivative of this eigenvalue along the direction of the curve is negative. This can be easily understood if one considers the sign change of the eigenvalues which belong to the eigenvectors of the projected Hessian orthogonal to the curve along the IRC. At the transition states, every eigenvector of the projected Hessian is an eigenvector of the Hessian. At TS1, the IRC curve starts along the transition vector and all the eigenvectors orthogonal to the curve of the projected Hessian have positive eigenvalues. At TS2, the IRC curve has a direction orthogonal to the transition vector. Therefore, this vector is a projected Hessian eigenvector orthogonal to the curve whose eigenvalue is negative. This eigenvalue changes from positive at TS1 to negative at TS2 and therefore it follows that the eigenvalue must have zero value at some point along the IRC. This is the simple idea that lies behind the Bolzano theorem.

To locate the bifurcation point, we have used a program developed by us[17] in conjuction with the Gaussian 98 package.[13] In this algorithm, the Hessian is projected to the subspace orthogonal to the IRC curve. To achieve sufficient accuracy, the Hessian at the first point of the IRC was calculated analytically every ten IRC points. By this way it was possible to locate the turning point of the eigenvector of interest. This eigenvector corresponds to the not totally symmetric vibrational coordinate of the Cope rearrangement.

The system runs along the IRC of C_2 symmetry from TS1, passes a VRI, and reaches a second transition state, TS2, of C_{2v} symmetry. From TS2, the molecule will decay to the C_s symmetry energy minimum of SBV (Figure 1). Therefore, with the help of the bifurcation, we have shown the existence of a "concerted pathway" for the interconversion of COT and SBV, and this pathway is connected to the degenerate Cope rearrangement of SBV. We have also established the intrinsic relationship between both processes, which until now were considered to be independent.

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[14] The G2(MP2) and G2 procedures were introduced by Pople and coworkers[15, 16] with the purpose of making reliable theoretical predictions. The two methods differ in their implementation of additivity approximations but each corresponds effectively to calculations at the QCISD(T)/6-311 + G(3df,2p) level with MP2(full)/6-31G(d) optimized geometries. Scaled HF/6-31G(d) zero-point vibrational energies and higher level corrections accommodate the remaining deficiencies.

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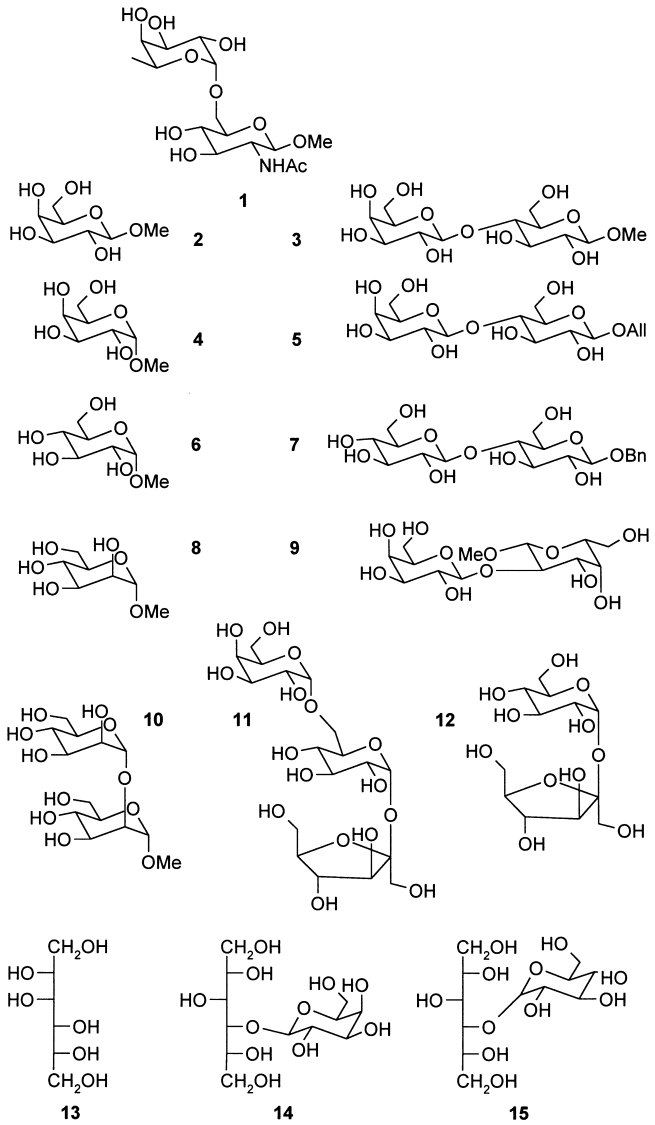
[17] This procedure will be published elsewhere with another examples of VRI from the $(CH)_8$ family of isomers.

Application of 3D-TOCSY-trNOESY for the Assignment of Bioactive Ligands from Mixtures**

Lars Herfurth, Thomas Weimar, and Thomas Peters*

An increasing body of work demonstrates that NMR spectroscopy provides powerful protocols to screen compound mixtures such as combinatorial libraries for their binding activity towards receptor proteins.[1–5] Compared to other screening techniques, NMR has specific advantages. One important feature is that NMR experiments allow parallel screening protocols without the need to subsequently separate the library components. In addition, NMR potentially delivers precise structural and topological information on the bioactive ligand, the protein binding site, or both. A comparison of NMR screening protocols published so far shows that two main classes of experiments may be distinguished. One category of experiments targets primarily the receptor protein and aims at identifying those amino acids involved in binding. For instance, specific absorption rate measurements, "SAR by NMR", employs ^{15}N labeling of the proteins to allow for fast heteronuclear single quantum coherence (HSQC) experiments.[2] Another class of experiments relies on changes of specific ligand properties upon binding to a receptor protein. In the main, altered relaxation, diffusion, or both have been utilized as the basis for such experiments.[3] It has been recently shown that saturation transfer difference (STD) experiments are especially useful for identifying ligands with binding activity and, furthermore, deliver information on the binding epitope.[4]

Herein, we report on a library consisting of 15 individual carbohydrates (Scheme 1) in the presence of the lectin *Aleuria aurantia* agglutinin (AAA). We have already shown



Scheme 1. Components of the library tested for the binding activity towards AAA. All components are present in approximately 10 mM concentration with a binding site:ligand ratio of 1:20 for each. Details of the sample preparation have been described previously.[5a]

that transfer NOE spectroscopy (trNOESY) experiments deliver typical cross-peak patterns that allow assignment of the bioactive component if all individual compounds are known.[5a] However, without this prior knowledge, an unambiguous assignment would be impossible. In the following, we present a strategy that closes this gap.

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