Valence Isomerization of Cyclohepta-1,3,5-triene and its Heteroelement Analogues
1.1 Introduction

Valence isomerization of cyclohepta-1,3,5-triene (1) into bicyclo[4.1.0]hepta-2,4-diene (2) has captured the attention of chemists for over five decades.\cite{1} This interest extended to the related heterocyclic compounds 3–8, bearing one oxygen, sulfur or nitrogen atom, after the discovery of their biological importance\cite{2} (Scheme 1). In contrast, phosphane analogue 9 and phosphanorcaradiene 10 have received only limited attention with their application as phosphinidene precursor being the most notable.\cite{3,4} Because the synthesis and isolation of the parent and substituted heteropines 5, 7, 9 remains challenging, computational chemistry has played an important role in understanding their chemical properties.

Reviewing the influence of the heteroelement on the cycloheptatriene–norcaradiene valence isomerization necessitates a brief overview of the parent all-carbon system. This will be followed by examining the experimental data on the heteropine valence isomerization in conjunction with the computed geometrical and aromaticity features of the parent isomers. Whereas it is not the focus of this review, selected examples of substituted heteropines and their synthesis will be given.

\[ \begin{align*}
1 & \quad X = \text{CH}_2 \\
3 & \quad X = \text{O} \\
5 & \quad X = \text{S} \\
7 & \quad X = \text{NH} \\
9 & \quad X = \text{PH}
\end{align*} \]

\[ \begin{align*}
2 & \quad X = \text{CH}_2 \\
4 & \quad X = \text{O} \\
6 & \quad X = \text{S} \\
8 & \quad X = \text{NH} \\
10 & \quad X = \text{PH}
\end{align*} \]

Scheme 1. Valence isomerization of cyclohepta-1,3,5-triene (1) and its heteroelement analogues.
1.2 Cycloheptatriene Valence Isomerization

Cyclohepta-1,3,5-triene (1), first isolated in 1883\[^5\], has a boat shaped conformation, as determined by electron diffraction\[^6\], a microwave study\[^7\], and an X-ray structure analysis of its derivative thujic acid\[^8\], but these methods give different tilt angles $\alpha$ and $\beta$ (see Scheme 2). More accurate data on the geometrical features of 1, come from a B3LYP/6-311+G(d,p) study that gave an $\alpha$ angle of 52.9° and a $\beta$ angle of 25.4°\[^9,10\].

Low temperature $^1$H NMR measurements showed that the slightly homo-aromatic boat conformation undergoes a degenerate ring flip via an anti-aromatic C$_{2v}$ transition state with a free energy barrier of 5.7 kcal mol$^{-1}$ in CBrF$_3$\[^11\] and 6.3 kcal mol$^{-1}$ in CF$_2$Cl$_2$\[^12,13\].

\[ \begin{array}{c}
\beta \\
\text{X} \\
\end{array} \begin{array}{c}
\alpha \\
\text{X} \\
\end{array} \rightleftharpoons \begin{array}{c}
\text{C} \\
\text{C} \\
\end{array} \rightleftharpoons \begin{array}{c}
\text{C} \\
\text{C} \\
\end{array}
\]

Scheme 2. Conformational ring inversions.

Cycloheptatriene 1 is in equilibrium with bicyclo[4.1.0]hepta-2,4-diene (2) via a Woodward-Hoffmann symmetry-allowed disrotatory ring closure\[^14\]. Although the equilibrium strongly favors the seven-membered ring, the presence of small quantities of the bicyclic isomer 2 was inferred by Diels-Alder trapping reactions\[^15\]. In 1981, Ruben was the first to directly observe norcaradiene 2 employing low-temperature photolysis\[^16\]. He determined an activation barrier of 11±2 kcal mol$^{-1}$ for the formation of 2 and a free energy difference between the isomers of about 4 kcal mol$^{-1}$\[^16\]. Strong electron-withdrawing groups at the methylene bridge influence the equilibrium in favor of the norcaradiene isomer, as is the case for the thermally stable 1,1-dicyano-derivative\[^17\]. At the B3LYP/6-311+G(d,p) level of theory, the geometry of the parent norcaradiene was shown to have a straighter bow ($\alpha = 65.8^\circ$) but flatter stern ($\beta = 18.9^\circ$) as compared to cyclohepta-1,3,5-triene\[^9\].
In addition to the 1→2 interconversion, the parent C\textsubscript{7}H\textsubscript{8} has a rich rearrangement chemistry (Scheme 3). In 1957, Woods observed the rearrangement of bicyclo[2.2.1]hepta-2,5-diene (12) into cycloheptatriene 1, which was postulated to proceed via diradical 11 and norcaradiene 2.\textsuperscript{[18]} Instead pyrolysis of 1 yields toluene by a [1,3]-H shift.\textsuperscript{[19]} Norcaradiene 2 can also undergo a [1,5]-carbon “walk” as was discovered by Berson and Willcott in 1965.\textsuperscript{[20]} Although, this process should proceed with retention of configuration according to the Woodward-Hoffmann rules, studies of optically active substituted cycloheptatrienes showed that the “forbidden” path is favored so that the walk occurs with inversion of configuration.\textsuperscript{[21,9]} The fourth and last rearrangement, a [1,5]-hydrogen shift, was discovered by a high-temperature NMR study of hydrogen isotopomers of cycloheptatriene. At 100–140 °C, 1 undergoes suprafacial [1,5]-H shifts with an activation energy of approximately 31 kcal mol\textsuperscript{-1} (Scheme 3).\textsuperscript{[22,23]}

\begin{center}
\includegraphics[width=\textwidth]{Scheme_3.png}
\end{center}

\textit{Scheme 3.} Rearrangements of the parent cycloheptatriene 1 and norcaradiene 2.

1.3 Valence Isomerization of Heteropines

1.3.1 Oxepine / Benzene oxide

Oxepine (3) was first isolated in 1964 by Vogel \textit{et al.} by double dehalogenation of 1,2-dibromo-4,5-epoxycyclohexane.\textsuperscript{[24]} Oxepine can also be synthesized by epoxidation of Dewar benzene followed by photolytic or thermal ring
expansion.\textsuperscript{[25]} In contrast to the cycloheptatriene–norcaradiene (1–2) pair, the equilibrium constant for oxepin 3 and 7-oxa-bicyclo[4.1.0]hepta-2,4-diene (4, benzene oxide) varies widely with solvent polarity and to some extent with temperature, making it possible to work with solutions highly enriched with either one of the two isomers.\textsuperscript{[24b,26]} The facile 3–4 valence isomerization\textsuperscript{[27a,28,29]} is of considerable interest as arene oxides are intermediates in the oxidative metabolism of aromatic substrates.\textsuperscript{[30]} In addition, also photo-oxidation of benzene creates this isomeric pair.\textsuperscript{[31]}

Using \textsuperscript{1}H NMR spectroscopy, Vogel and Günther determined that bicyclic benzene oxide 4 is 1.7 kcal mol\textsuperscript{−1} more stable than monocyclic 3 in apolar solvents\textsuperscript{[24b,32]} with an activation barrier for the conversion from 4 to 3 of 9.1 kcal mol\textsuperscript{−1} and 7.2 kcal mol\textsuperscript{−1} for the reverse reaction. Calculations at QCISD(T)/6-31G(d) confirm the bicyclic isomer to be the most stable one, albeit with a very small energy difference of only 0.1 kcal mol\textsuperscript{−1} with a barrier for interconversion of 9.1 kcal mol\textsuperscript{−1}.\textsuperscript{[35]} By changing to more polar solvents, the oxepine isomerization equilibrium shifts further toward benzene oxide (more positive $\Delta G$), suggesting a larger dipole moment for benzene oxide than for oxepine. Methyl substitution at the 2- and 7-positions reverses the stability order, rendering the oxepine as the energetically favored isomer due to the destabilizing eclipsing of the two methyl groups in benzene oxide 4.\textsuperscript{[24,35]}

\begin{center}
\begin{tikzpicture}
\tikzstyle{every node}=[font=\small]
\tikzstyle{reaction}=[baseline=-0.5ex]
\node[reaction,fill=white] (A) at (0,0) {\textbf{3}}; \node[reaction,fill=white] (B) at (2,0) {\textbf{4}}; \node[reaction,fill=white] (C) at (0,-1) {\textbf{13}}; \node[reaction,fill=white] (D) at (2,-1) {\textbf{14}};
\draw[reaction,->] (A) -- (B) node[midway,above] {{H, H\textsubscript{2}}}; \draw[reaction,->] (C) -- (D) node[midway,above] {\text{hv}};
\draw[reaction,->,shorten >=1ex] (A) -- (C) node[midway,above] {{hv}}; \draw[reaction,->,shorten >=1ex] (B) -- (D) node[midway,above] {\text{hv}};
\end{tikzpicture}
\end{center}

\textbf{Scheme 4.} Reactivity of oxepine (3) and benzene oxide (4).
Depicted in Scheme 4 are the most important reactions that the parent oxepine (3) and benzene oxide (4) can undergo. Irradiation of oxepine results in ring contraction yielding 2-oxabicyclo[2.3.0]hepta-3,6-diene (13).\cite{24} Under thermal, photochemical or acidic conditions, the three-membered ring of bicyclic 4 opens generating phenol,\cite{24a,33} in analogy to the all-carbon norcaradiene 2 that gives toluene. In addition, 4 undergoes highly selective Diels-Alder reactions with N-phenylmaleimide and dimethylacetylenedicarboxylate providing single anti-adducts (e.g. 14; Scheme 4).\cite{31b,34} Calculations on model structures show that the anti cycloadditions are kinetically controlled, although syn addition is thermodynamically favored.\cite{35}

### 1.3.2 Thiepine / Benzene sulfide

The parent thiepine (5) is 7.0 kcal mol\(^{-1}\) less stable than benzene sulfide (6). This energy difference is much larger than for the oxygen homologues because sulfur is better accommodated in three-membered rings.\cite{35} Nevertheless, bicyclic 6 has never been isolated due to the low activation barrier for sulfur extrusion,\cite{35,36,37} which occurs via a sequence of low energy reactions involving several sulfur-containing intermediates.\cite{38,39}

Thiepine 5 can be stabilized by Fe(CO)\(_3\)-complexation (15)\cite{40} or by decorating the seven-membered ring with substituents. The first isolated metal-free thiepine (16) was reported in 1974 by Reinhoudt and Kouwenhoven using electron-withdrawing groups to delocalize the \(\pi\)-electrons of the thiepine ring, but this species still eliminates sulfur at room temperature.\cite{41} With the synthesis of the sterically shielded 2,7-di-\textit{tert}-butylthiepine 17, a relatively simple and thermally stable thiepine was obtained allowing experimental studies on its chemical and physical properties.\cite{42} The thermally robust dibenzo[\textit{b,\textit{f}}]thiepines are of interest for their potent biological activity, which is illustrated by the psycho sedative and antipsychotic properties of zotepine (18).\cite{27c,43,44}
1.3.3 1H-Azepine / Benzene imine

The parent 1H-azepine (7)\textsuperscript{[45]} was first generated in 1963 by Hafner after hydrolysis of ethyl-1H-azepine-N-carboxylate with potassium hydroxide and subsequent protonation.\textsuperscript{[46]} Because 1H-azepine is highly unstable and rearranges to 3H-azepine via a [1,3]-H shift, its characterization was accomplished 17 years later at \(-78^\circ\text{C}\) by Vogel \textit{et al.}\textsuperscript{[47,48]} N-substitution stabilizes the 1H-azepine. As for the all-carbon analogues, the valence isomerization equilibrium strongly favors the monocyclic form, which was estimated at 7.9 kcal mol\(^{-1}\) at B3LYP/6-31G(d) for the parent system (7 \(\rightleftharpoons\) 8).\textsuperscript{[49]} Also low temperature \(^1\)H and \(^{13}\)C NMR measurements on 19 display only small amounts of the bicyclic isomers 20 (Scheme 5).\textsuperscript{[48,50]}

The reluctance to form the bicyclic isomer dictates the reactivity of azepines as they exhibit the characteristics of cyclic polyene chemistry, which is illustrated by the ability of the monocyclic isomer to undergo cycloadditions as 2\(\pi\) (\(\rightarrow\) 21).\textsuperscript{[51]}

\begin{center}
\textbf{Scheme 5.} Valence isomerization of 1H-azepines.
\end{center}
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$4\pi \rightarrow 22^{[51,52]}$ or $6\pi \rightarrow 23, 24^{[53]}$ component (Scheme 6). In addition, azepine 7 rearranges photochemically to bicyclic $25^{[54]}$ and in the presence of an acid yields aniline derivatives $26^{[55]}$ in analogy to the cycloheptatriene and oxepine.$^{[56]}$

Scheme 6. Reactivity of $1H$-azepine.

Azepines have received considerable attention because of their biological importance and pharmaceutical relevance.$^{[57]}$ For instance, $3H$-$3$-benzazepin-$2$-amines 27 possess antihypertensive activity$^{[58]}$ and all tricyclic dibenzo[bf]azepines (e.g., 28) bearing a basic side chain affect the central nervous system.$^{[59]}$

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1.3.4 1H-Phosphepine / Benzene phosphane

Although the parent 1H-phosphepine (9) and its 2.5 kcal mol\(^{-1}\) more stable valence isomer benzene phosphane (10)\(^{[60]}\) have never been isolated, there is evidence for the existence of the parent phosphatropylium ion (29), which was generated in the gas phase by collision activation between PI\(_3\) and benzene.\(^{[61]}\) The thermal instability of the phosphepines is due to the facile decomposition of its bicyclic isomer 10 into benzene and phosphinidene R–P.\(^{[62]}\) However, the 7-membered ring can be stabilized by phosphorus oxidation (30),\(^{[62]}\) the introduction of bulky substituents at the 2 and 7 positions (33),\(^{[63]}\) or benzannulation (e.g. 3H-benzophosphepine 32).\(^{[3c,64]}\)

![Image of chemical structures](image)

The thermal lability of the transition metal-complexed 3H-benzophosphepine 33 has been explored by Lammertsma et al. for the synthesis of a variety of organophosphorus compounds by means of [1+2]-cycloadditions of the \textit{in situ} generated singlet phosphinidene 35 with olefins or acetylenes (Scheme 7).\(^{[3,4]}\)

![Scheme 7](image)

\(33 \xrightarrow{M(CO)\_5, \geq 60^\circ C} 34 \quad 35 \quad M = \text{Cr, Mo, W}; \quad R = \text{e.g. Me, Ph}\)

\textbf{Scheme 7.} Phosphinidene generation from metal-complexed benzophosphepine 33.
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1.4 Geometry and Boat Inversion

Determining the conformations of the heteropines has been a challenge, since only the parent oxepine (3) can be isolated as a liquid at room temperature. Although spectroscopic measurements indicated a boat shape for the monocyclic structures with alternating C=C bond lengths, attempts for more exact measurements came from single-crystal X-ray structure analysis of simple derivatives, later complemented by high-level calculations on the parent systems (see Table 1). Determining the conformation for the bicyclic norcaradienes is far more challenging and currently depends solely on calculations.

Table 1. Summary of the relative energies (kcal mol\(^{-1}\)) of isomerization from the parent bicyclic forms norcaradiene (NCD) 2 (C), 4 (O), 6 (S), 8 (N), 10 (P) to the monocyclic cycloheptatrienes (CHT) 1 (C), 3 (O), 5 (S), 7 (N), 9 (P)) and their ring inversion.\(^{[a]}\)

<table>
<thead>
<tr>
<th></th>
<th>NCD</th>
<th>TS</th>
<th>CHT</th>
<th>TS(_{inv})</th>
<th>Method</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>C (1,2)</td>
<td>4</td>
<td>11(^{[c]})</td>
<td>0.0</td>
<td>~6</td>
<td>Exp</td>
<td>[11,12,16]</td>
</tr>
<tr>
<td>O (3,4)</td>
<td>0.0</td>
<td>9.1(^{[b]})</td>
<td>1.7</td>
<td>–</td>
<td>Exp</td>
<td>[24b,32]</td>
</tr>
<tr>
<td></td>
<td>0.0</td>
<td>7.0</td>
<td>0.1</td>
<td>3.5</td>
<td>QCISD(T)/6-31G(d)</td>
<td>[35]</td>
</tr>
<tr>
<td>S (5,6)</td>
<td>0.0</td>
<td>20.5(^{[b]})</td>
<td>7.0</td>
<td>7.3</td>
<td>QCISD(T)/6-31G(d)</td>
<td>[35]</td>
</tr>
<tr>
<td>N (7,8)</td>
<td>7.9</td>
<td>11.4(^{[c]})</td>
<td>0.0</td>
<td>~3</td>
<td>B3LYP/6-31G(d)</td>
<td>[49,65]</td>
</tr>
<tr>
<td>P (9,10)</td>
<td>0.0</td>
<td>15.7</td>
<td>2.5</td>
<td>5.2</td>
<td>B3LYP/6-311+G(d,p)</td>
<td>[60]</td>
</tr>
</tbody>
</table>

\(^{[a]}\) Gibbs free energies for experimental data (first two entries) and enthalpies for computational data. \(^{[b]}\) Equilibrium from NCD to CHT. \(^{[c]}\) Equilibrium from CHT to NCD.

The molecular structure of the simple 2-tert-butoxycarbonyl oxepine (36) shows a boat configuration with bow (\(\alpha\)) and stern (\(\beta\)) fold angles of 56.5 ° and 26.0 °, respectively,\(^{[66]}\) making it slightly more curved than cyclohepta-1,3,5-triene (1; \(\alpha = 52.9 \, ^\circ\), \(\beta = 25.4 \, ^\circ\)).\(^{[9]}\) This structure differs little from the MP2/6-31G(d) optimized geometry of the parent oxepine (3) (\(C_s\) symmetry; \(\alpha = 58.3 \, ^\circ\), \(\beta = 30.8 \, ^\circ\)) and
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illustrates that the tert-butoxycarbonyl substituent hardly influences the geometry. A single-crystal X-ray analysis for sulphur analogue 2,7-di-tert-butylthiepine (17) shows on the other hand a less curved structure ($\alpha = 49.6^\circ$ and $\beta = 28.0^\circ$), which was supported by an MP2/6-31G(d) optimized geometry of the parent thiepine 5 ($\alpha = 50.3^\circ$ and $\beta = 30.8^\circ$).

The molecular structure of N-substituted azepine 37 displays a shallower boat structure ($\alpha = 43.4^\circ$ and $\beta = 21.6^\circ$). This behavior is solely due to the N-substituent as the CASSCF/3-21G optimized geometry shows a more curved $\beta$ angle of 36.4° for the parent 7. For the P analogues, the single-crystal X-ray structure analysis of a (OC)$_2$W-complexed, benzannulated phosphepines 33 (Scheme 7) also shows a flattened boat conformation ($\alpha = 40.5^\circ$, $\beta = 28.2^\circ$) compared to the computed parent structure that is more curved ($\alpha = 48.3^\circ$, $\beta = 27.8^\circ$).

Although the boat form prevails in all monocyclic heteropines, Cremer et al. indicated that this presents an incomplete picture. They determined that the parent 1, 3 and 5 posses at least 22% chair character, leading to an almost constant boat puckering for the cycloheptatrienes. By studying the racemization of substituted benzene oxides (Scheme 2), the oxepine ring inversion barrier was estimated at 6.5 kcal mol$^{-1}$ at 135 K, which is similar 4.5 kcal mol$^{-1}$ calculated for the parent oxepine (3) at QCISD(T)/6-31G(d). The barrier for thiepine 5 is with 8.3 kcal mol$^{-1}$ nearly twice as large (same level of theory), probably because the flattened thiepine ring leads to higher antiaromatic destabilization. The interconversion of the boat forms of the azepines and phosphepines is also facile, requiring only 3 (N) and 5.2 kcal mol$^{-1}$ (P), respectively.
1.5 Aromaticity

One of the issues in the cyclohepta-1,3,5-triene valence isomerization has been whether the heteropines display aromaticity. The flattened transition structure for ring inversion (Scheme 2) bears $8\pi$-electrons and should display antiaromaticity according to the Hückel theory and, in fact, the inherent instability of thiepine 5 has been ascribed to this.\textsuperscript{[70]} However, the monocyclic boat-shaped structures can exhibit homoaromaticity by conjugative interaction of the triene part through 1,6-overlap of 2p$\pi$-orbitals,\textsuperscript{[65]} as is the case for cyclohepta-1,3,5-triene (1).\textsuperscript{[13]} With the use of nucleus-independent chemical shifts (NICS(1)),\textsuperscript{[71]} it has been shown that thiepine (−2.3 ppm)\textsuperscript{[72]} and phenylphosphepine (−4.8 ppm)\textsuperscript{[3c]} indeed display aromatic character when compared to the well-known six $\pi$-electron Hückel-aromatic tropylium cation,\textsuperscript{[71]} which has a NICS(1) value of −8.2 ppm. Adding electronegative substituents enhances the effect and fully aromatic systems are obtained after complete fluorination of the heteropines.\textsuperscript{[37]} In contrast, the flattened transition structures for ring inversion of thiepine and phosphepine are indeed highly antiaromatic, with positive NICS(1) values of 19.3\textsuperscript{[72]} and 6.4 ppm,\textsuperscript{[3c]} respectively.

\begin{align*}
\text{NICS(0)} & \quad -5.7 \text{ ppm} \quad -8.0 \text{ ppm} \quad -9.5 \text{ ppm} \quad -7.9 \text{ ppm}
\end{align*}

1.6 Summary

Valence isomerization of cyclohepta-1,3,5-triene into bicyclo[4.1.0]hepta-2,4-diene and their corresponding heteroelement analogues have been reviewed giving insight into the chemical and physical properties of these fascinating species.
1.7 References and Notes


[10] For similar computational geometrical studies, see: a) \( \alpha = 52.1^\circ, \beta = 25.2^\circ \) determined at the CASSCF(6,6)/6-31G(d) level; A. A. Jarzęcki, J. Gajewski, E. R. Davidson, J. Am. Chem. Soc. 1999, 121, 6928–6935. b) \( \alpha = 57.5^\circ, \beta = 27.6^\circ \)


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[56] For more details on azepines, see ref 27b.


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[71] The NICS value is obtained from NMR calculations of a ghost atom (Bq) at the geometrical ring center (NICS(0)), but the value 1 Å above the ring (NICS(1)) is recommended, because lack of σ shielding makes it a better measure of π-electron delocalization. Z. Chen, C. S. Wannere, C. Corminboeuf, R. Puchta, P. v. R. Schleyer, *Chem. Rev.* **2005**, *105*, 3842–3888.