Examination of the Valence Tautomers Benzene Oxide and Oxepin and Two Derivative Systems by *ab Initio* Methods

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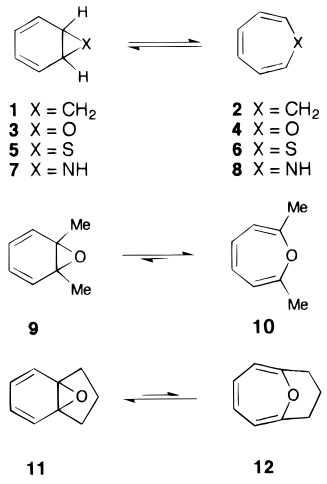
The enthalpies of the valence tautomerism between benzene oxide **3** and oxepin **4** and of benzene sulfide **5** and thiepin **6** are estimated from post-Hartree−Fock *ab initio* calculations (QCISD(T)/6-31G*//MP2/6-31G*) to be 0.59 kJ mol^{-1} and 29.32 kJ mol^{-1}, respectively. The latter value is larger due to a combination of greater stability of the sulfide relative to the oxide and of the relative instability of thiepin compared to oxepin. For the dimethyl analog of the benzene oxide/oxepin system (**9** and **10**) the ΔH at the same level is −6.73 kJ mol^{-1}. The calculated molecular orbital energies are in linear relationship to those available from photoelectron spectra and suggest reassignment in some cases. The structures of the transition states for the conformational inversion of oxepin and of thiepin are shown to be planar, and the QCISD(T) enthalpies of inversion are 14.5 and 30.5 kJ mol^{-1}, respectively. Barriers to tautomerization are estimated to be 29.4 and 85.7 kJ mol^{-1}, respectively, for the oxide and the sulfide. Protonation stabilizes the oxide form *versus* the oxepin. The high level of facial selectivity seen in the Diels−Alder reactions of **3** is shown to be consistent with higher angular strain in *syn* addition.

Introduction

There has been considerable experimental and theoretical interest in the valence tautomers norcaradiene **1** and 1,3,5-cycloheptatriene **2** and the related pairs of heterocyclic compounds **3**−**8**. The oxygen-containing system of benzene oxide **3** and oxepin **4** has received the most attention. It was first



synthesized by Vogel in 1964,[1] and almost two decades later benzo-fused analogs of these were suggested as metabolites of polycyclic aromatic hydrocarbons.[2] Vogel and Günther[3,4] showed, using ^{1}H NMR and UV, that the proportion of **3**, relative to **4**, increased with decreasing temperature and with increasing solvent polarity. Analogs were also examined. Steric interaction between the methyl groups in **9** was thought to destabilize this form relative to the oxepin **10**, but ring strain greatly destabilized the bicyclic oxepin derivative **12** *versus* **11**.[4]

MINDO/3 and *ab initio* studies at the STO-3G level established that neither aromatic stabilization nor antiaromatic destabilization plays an important role in influencing the

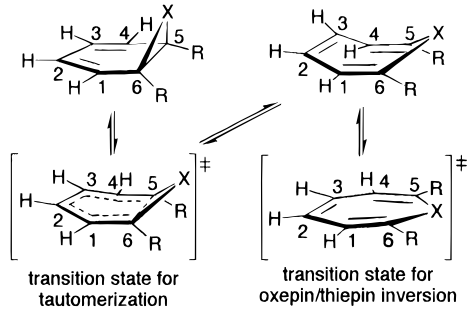


Figure 1. Tautomerization and inversion of oxepin/thiepin.

energetics of the valence tautomerism with **3** and **4**.[5] In conjunction with a recent photoelectron study, the structure of **3** at the HF/3-21G level was obtained.[6] However, Bock *et al.*[7] had shown that geometries and enthalpies are poorly estimated at lower levels of theory. They optimized the structures of **3** and **4** at the 6-31G, 6-31G*, and AM1 levels, and they carried out single-point post-Hartree−Fock calculations (MP2 and MP3) using these structures, but they did not address the transition states for the valence tautomerization and the conformational inversion of the oxepin (Figure 1). In this paper, we provide accurate geometrical and energy data from post-Hartree−Fock calculations for structures and transition states involving **3**, **4**, **9**, and **10**.

The simplest sulfur-containing system of benzene sulfide **5** and thiepin **6** remains an elusive synthetic target, although substituted and benzo-fused thiepins have been prepared.[8,9] In spite of their theoretical interest, these compounds have received scant computational attention. To our knowledge, only data at the MNDO and STO-3G levels have been reported,[5c,8] in conjunction with a photoelectron study of substituted thiepins.[8] Reported below are the results of calculations on **5** and **6** at a high level of theory.

Finally, herein we reveal, based on *ab initio* calculations, the origin of the remarkable degree of facial selectivity that we reported previously for Diels−Alder reactions with **3**.[10]

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TABLE 1: Energies of Tautomerization from the Benzene Oxide/Sulfide to the Oxepin/Thiepin Forms and for the Inversion of the Oxepin/Thiepin at Various Levels of Theory

	energy[a]								
	benzene oxide/oxepin (**3**/**4**)			dimethyl analog (**9**/**10**)			benzene sulfide/thiepin (**5**/**6**)		
basis set or property	**3**−**4**	tautomer.[b]	inversion[c]	**9**−**10**	tautomer.[b]	inversion[c]	**5**−**6**	tautomer.[b]	inversion[c]
HF/6-31G*//HF/6-31G*	−12.05	60.23	12.23	−28.85	61.03	16.19	29.79	129.91	26.76
MP2/6-31G*//HF/6-31G*	13.86	19.81	20.72	3.30	17.63	26.14	47.58	76.36	40.33
MP2/6-31G*//MP2/6-31G*	13.90	26.50	24.74	2.10	22.37	30.68	44.15	79.49	43.54
MP2/6-31+G*//MP2/6-31G*	13.05	23.27	28.01				38.27	72.51	47.76
MP2/6-311G*//MP2/6-31G*	9.20	19.17	26.67				44.46	72.55	47.41
MP3/6-31G*//MP2/6-31G*	2.85	41.97	18.13	−8.54	44.11	22.76	37.12	106.30	33.13
MP4/6-31G*//MP2/6-31G*	5.41	32.71	17.42	−3.63	32.73	23.71	34.70	85.85	35.17
QCISD(T)/6-31G*//MP2/6-31G*	1.43	36.07	15.60	−7.33	38.33	21.51	31.85	92.72	31.96
enthalpy (at 298 K)	0.59	29.38	14.47	−6.73	32.88	19.86	29.32	85.69	30.51
entropy (at 298 K)	8.34	−3.02	−15.09	8.05	2.25	−17.58	6.68	−4.66	−15.14

[a] kJ mol^{-1}, except for entropy: J mol^{-1} K^{-1}. [b] Activation energy from the oxide/sulfide to the transition state for valence tautomerization. [c] Activation energy from the oxepin/thiepin in its preferred, boat-like conformer to the planar transition state for its inversion.

Method

Geometries of **3**, **4**, **9**, **10**, **5**, and **6** and their transition states were optimized at the Hartree−Fock 6-31G* level[11] with the program MUNGAUSS[12] and at the second-order Møller−Plesset (MP2/6-31G*) level (frozen core)[13] with Gaussian 92.[14] Minima and the planar forms of **4**, **6**, and **10** were optimized using Davidon's optimally conditioned method[15] with C_s or C_{2v} symmetry constraints, as appropriate. Incompletely converged structures were further optimized by the DIIS method of Pulay.[16] The transition states in the Diels−Alder study were located at the 6-31G* level with MUNGAUSS. The structures of the transition states for the tautomerization of **3** and **4** and for the Diels−Alder reactions were optimized using a minimization of sum-of-squares method.[17] Calculations MP2/6-31+G*//MP2/6-31G*,[18] MP2/6-311G*//MP2/6-31G*,[19] and MP4SDTQ/6-31G*//MP2/6-31G* (hereafter referred to as "MP4") levels were performed with either GAMESS[20] or Gaussian 92. The highest level of calculation was QCISD(T)/6-31G*//MP2-FC/6-31G* (hereafter "QCISD(T)"),[21] with frequencies calculated at HF/6-31G*, using Gaussian 92. Calculated enthalpies, entropies and values for $\Delta G^{\ddagger}$ are given at 298 K using unscaled frequencies.

Results and Discussion

A. Thermodynamics. Table 1 presents pertinent *ab initio* energy data for the benzene oxide **3**−oxepin **4** system, their dimethyl analogs **9** and **10**, and the benzene sulfide **5**−thiepin **6** system.

The results of our calculations confirm a considerable variation with both basis set, which Bock had noted,[7] and electron correlation. Vogel and Günther[3] had determined by ^{1}H NMR that **3** is 7 kJ mol^{-1} lower in enthalpy than **4**. Only bands attributable to **3** appear in the (gas phase) photoelectron spectrum of the same tautomeric system.[6] The computed enthalpy favors **3**, but the difference is very small, 0.59 kJ mol^{-1} at QCISD(T). Furthermore, the relative stability of **3** may still be overestimated at this level. Application of the additivity rule using our MP4 result would predict an MP4/6-31+G* ΔH of −3.72 kJ mol^{-1} and an MP4/6-311G* ΔH of −0.13 kJ mol^{-1}, and using the QCISD(T) result, the predictions are −0.26 kJ mol^{-1} for QCISD(T)/6-31+G* and −4.11 kJ mol^{-1} for QCISD(T)/6-311G*. Comparing the MP2/6-31G*//HF/6-31G* and the MP2/6-31G*//MP2/6-31G* results (Table 1), it is obvious that with these tautomers it is not necessary to optimize at the correlated level in order to obtain accurate enthalpies. Thus, the importance of correlation in establishing energies in these systems cannot be ascribed to small differences in geometry. Differences between experiment and calculation can be expected due to solvation effects in the former because Vogel's work[3,4] demonstrated significant differences between solvents.[22] We calculate the entropy change for **3** → **4** to be 8.34 J mol^{-1} K^{-1} (HF/6-31G*). The only experimental estimates available (44 ± 35 and 46 ± 21 J mol^{-1} K^{-1}) with which our calculation might be compared are from solution measurements.[4]

An adverse steric effect of propinquity of the methyl groups in **9** should lead to a more negative ΔH for **9** and **10**. QCISD(T) calculations indicate that dimethyloxepin **10** is more stable than the oxide form **9** by 6.73 kJ mol^{-1}, which is consistent with the experimental estimates[3a,10] and an early MINDO/3 treatment.[5b] The effect of the addition of correlation is especially large with these tautomers, with the difference between the ΔE at HF/6-31G*//HF/6-31G* and the ΔE at MP2/6-31G*//HF/6-31G* being over 32 kJ mol^{-1}. The entropy change is predicted to be 8.05 J mol^{-1} K^{-1}, which is very similar to the value for **3** → **4**.

The HF calculations show that benzene sulfide **5** is much more stable than is thiepin **6**, and the inclusion of correlation energy stabilizes **5** relative to **6** even further. At QCISD(T), ΔH is calculated to be 29.32 kJ mol^{-1}. Again, using additivity and the QCISD(T) data, we predict the QCISD(T)/6-31+G* ΔH to be 23.44 kJ mol^{-1} and the QCISD(T)/6-311G* ΔH to be 29.63 kJ mol^{-1}. Our high level computational results are in very marked contrast with the MNDO studies that had suggested only a very small preference (<1 kJ mol^{-1}) for **5**.[5c,8] The entropy change is calculated to be 6.68 J mol^{-1} K^{-1} (HF/6-31G*).

B. Geometry. Bond lengths, angles, and dihedrals from the MP2/6-31G* optimizations are given in Table 2. A number of interesting geometrical comparisons can be made from these data. The amounts of curvature (360° minus the C-1−C-6−C-5−O dihedral minus the C-2−C-1−C-4−C-5 dihedral) for **3** and for **4** are essentially the same. For the dimethyloxepin and the thiepin systems, the bicyclic tautomers (**9** and **5**) are less curved than the preferred, boat conformers of their corresponding oxepin **10** and thiepin **6** forms.

The effect of the steric interaction between the methyls in **9** is manifested not only in a larger C-1−C-6−C-5−CH_3 dihedral, relative to the C-1−C-6−C-5−H dihedral in **3**, but also, to a similar angular extent, by a flattening of the oxirane region (*viz.* the C-1−C-6−C-5−O dihedral) and an increase of the pucker in the diene moiety (*viz.* the C-2−C-1−C-4−C-5 dihedral).

Regarding the transition states for valence tautomerization (Figure 1), comparison of the C-1−C-2 and C-5−C-6 bond lengths and the C-1−C-2−C-3 and C-5−O (or S)−C-6 bond

TABLE 2: Calculated (MP2/6-31G*) Bond Lengths, Angles, and Dihedrals

	benzene oxide/oxepin					dimethyl analog			benzene sufide/thiepin			
	3	TS[a]	**4**	planar[b]	**9**	TS[a]	**10**	planar[b]	**5**	TS[a]	**6**	planar[b]
bond length (Å)												
C-5−H (or CH_3)	1.0897	1.0892	1.0884	1.0852	1.5077	1.5004	1.4930	1.4954	1.0879	1.0882	1.0874	1.0882
C-1−C-2	1.3602	1.4029	1.4465	1.4674	1.3570	1.3917	1.4441	1.4619	1.3565	1.3966	1.4476	1.4655
C-1−C-6	1.4598	1.3856	1.3488	1.3430	1.4699	1.4039	1.3531	1.3469	1.4667	1.3961	1.3528	1.3458
C-2−C-3	1.4443	1.3986	1.3637	1.3459	1.4436	1.4045	1.3643	1.3471	1.4472	1.4047	1.3648	1.3511
C-5−C-6	1.5188	1.9010	2.2477	2.4347	1.5206	1.8473	2.2703	2.4871	1.4878	2.0576	2.6458	2.8595
C-5−O (or S)	1.4423	1.3995	1.3959	1.3848	1.4525	1.4109	1.4036	1.3949	1.8524	1.7647	1.7703	1.7671
angle or dihedral (deg)												
C-1−C-2−C-3	121.42	122.51	124.07	125.95	121.02	122.33	124.39	126.58	121.16	123.01	126.30	130.25
C-1−C-6−C-5	117.40	111.28	105.85	103.64	116.72	111.87	105.54	102.93	117.47	108.13	99.21	98.23
C-1−C-6−O (or S)	116.88	119.02	121.34	132.11	115.25	117.13	119.38	129.87	118.97	121.80	122.60	134.23
C-2−C-1−C-6	120.21	121.78	123.84	130.42	121.67	122.44	123.99	130.49	121.23	124.15	126.32	131.51
C-5−C-6−O (or S)	58.23	47.22	36.38	28.47	58.44	49.11	36.03	26.94	66.15	54.34	41.64	35.99
C-5−O (or S)−C-6	63.54	85.56	107.24	123.06	63.13	81.78	107.95	126.13	47.69	71.32	96.71	108.01
C-1−C-6−C-5−O (or S)	106.13	110.42	121.75	180.00	104.55	107.60	118.90	180.00	111.54	116.58	129.72	180.00
C-1−C-6−C-5−H (or CH_3)	152.76	148.42	149.16	180.00	154.28	154.02	152.01	180.00	145.75	138.74	140.95	180.00
C-2−C-1−C-4−C-5	168.74	156.71	152.98	180.00	171.33	159.72	153.72	180.00	175.78	156.52	149.72	180.00
curvature[c]	85.13	92.87	85.27	0.00	84.12	92.68	87.38	0.00	72.68	86.90	80.56	0.00

[a] Transition state for valence tautomerization. [b] Transition state for inversion of the oxepin/thiepin. [c] 360° minus C-1−C-6−C-5−O (or S) dihedral minus C-2−C-1−C-4−C-5 dihedral.

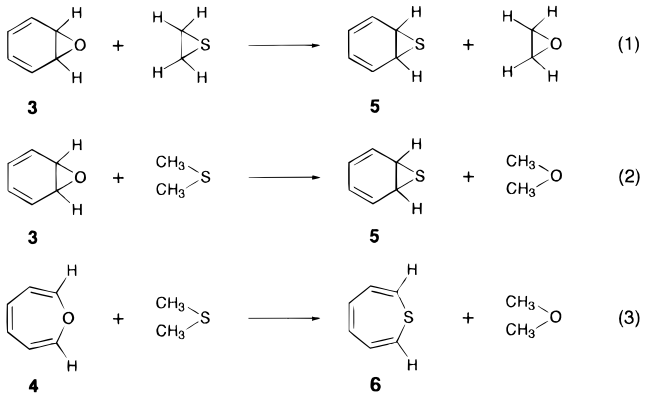


Figure 2. Isodesmic reactions involving **3**, **4**, **5**, and **6**.

angles suggests that the transition state is roughly midway between the two tautomeric forms. However, other parameters indicate that the geometrical changes are not synchronous. In all three systems, at the transition state the dihedral to the heteroatom (*i.e.*, C-1−C-6−C-5−O) is significantly closer to that of the bicyclic tautomer, whereas the diene pucker (C-2−C-1−C-4−C-5 dihedral) is much more similar to that of the oxepin/thiepin form. (Indeed, the tautomerization of **5** and **6** appears to be less synchronous than tautomerization of either oxygen system by this analysis.) A result of nonsynchronous tautomerization is that the transition state shows more curvature than either tautomer in all three systems.

The planar form of oxepin or thiepin is the transition state for its degenerate conformational inversion (Figure 1). In Table 1 one can see that the planar form of **4** is more stable than the planar form of **6**. This is because the longer carbon-to-heteroatom bonds in **6** cannot be completely accommodated by a smaller C-5−S−C-6 angle, so the strain on the C−C−C angles is greater in the planar form of **6** relative to the planar form of **4**.

C. Oxygen *versus* Sulfur Systems. The energetics (QCISD-(T)) of the three isodesmic reactions shown in Figure 2 allow a more complete comparison of the oxygen tautomers **3** and **4** with the sulfur tautomers **5** and **6**. Fusion of the three-membered heterocyclic ring into the bicyclic framework might be expected to lead to some $\pi-\sigma_{CX}$ mixing or to direct $\pi-n_X$ interactions, but in eq 1 the reactants are more stable than the products by only 3.9 kJ mol^{-1}. Therefore, either the stabilization associated with these phenomena is of similar magnitude with X = O or X = S or, what is more likely, these phenomena have little energetic impact in both systems. The latter is consistent with a similarity, evident in Table 2, in the bond lengths and angles for the nonheteroatomic portions of **3** and **5**. A recent photoelectron study of **3** also concluded that there is little $\pi-\sigma_{CO}$ or $\pi-n_O$ in mixing in **3**.[6] In eq 2, the products are more stable by 15.8 kJ mol^{-1}. This indicates that sulfur is accommodated in a three-membered ring better than oxygen, which is what should be expected with generally smaller substituent angles about sulfur. However, the relatively large difference in energy between benzene sulfide **5** and thiepin **6** is not only because of the stability of the sulfide **5** *versus* oxide **3** but also because of the relative instability of the thiepin **6** *versus* oxepin **4**. Our calculations indicate that the reactants in eq 3 are more stable by 14.7 kJ mol^{-1}. This difference can be ascribed to angle strain in the carbocyclic moiety of **6** that results from the longer C−S bonds. This is evidenced most clearly by the fact that in **6** the C-1−C-2−C-3 and C-2−C-1−C-6 bond angles are significantly larger than those in **4**, even though thiepin **6** still shows less curvature than **4** (see Table 2).

D. Ionization Energies. The first four molecular orbitals of **3** are calculated to have energies of 8.80, 10.78, 11.88 and 13.33 eV at the HF/6-31G* level and are described as π_-, $\pi_+ - \sigma_{CO}$, n_O, and $\pi_+ + \sigma_{CO}$, respectively. It is interesting to note that the π_+ portion mixes somewhat with the σ_{CO}. The first three bands of the photoelectron spectrum[6] are at 8.43, 10.20 and 11.45 eV and, assuming that these three bands are the π_-, $\pi_+ - \sigma_{CO}$, and n_O, give an excellent linear correlation (slope = 1.026, intercept = 0.195, $R^2 = 0.996$) with the calculation. This casts doubt upon the assignment of Modelli in which $\pi_+ - \sigma_{CO}$ and n_O are reversed.[6] The ionization energies at HF/3-21G provided by Modelli and co-workers also pointed to this assignment, but they argued, based upon comparisons with experimental data of similar compounds, that this could not be correct and surmised that HF/3-21G calculations must overestimate the stability of the σ_{CO} "orbital". HF/6-31G* describes the three-membered ring moiety much better than does HF/3-21G; nevertheless the ionization energies calculated at these levels are very similar. This suggests to us that the calculated assignment should now be accepted as the correct assignment.

The first four molecular orbitals of the still-unsynthesized benzene sulfide **5** are predicted to occur at 8.36, 9.16, 10.89,

and 12.15 eV. In contrast with **3**, an examination of these molecular orbitals indicates that in **5** there is more mixing of components of the three-membered ring with the π_-, and we describe the first molecular orbitals as $\pi - \sigma_{CS,-}$, n_S, $\pi_+ - \sigma_{CS,+}$, and $\sigma_{CS,-}$, respectively. Bands due to the oxepin **4** do not appear in Modelli's photoelectron spectrum of **3**, but we predict the first four molecular orbitals of **4** to lie at 8.10, 10.42, 11.78, and 13.06 eV (π'_4, π''_3, π'_2, and n_O, respectively). The first four molecular orbitals of thiepin **6** are predicted to lie at 8.19, 10.08, 10.32, and 11.64 eV (π'_4, π'_3, π''_2, and n_S, respectively). The first three appear to be very similar to those of oxepin except with an inversion of the second and third orbitals. The basic distribution of these orbitals is in good agreement with the photoelectron spectra of several substituted thiepins.[8] For example, a linear relationship (slope = 1.36, intercept −2.33, $R^2 = 0.988$) can be obtained by plotting the experimental ionization energies[8] for 2,7-di-*tert*-butylthiepin *versus* the calculated orbital energies for **6**.

E. Inversion of Oxepins and Thiepin. With oxepin **4**, the process of conformational inversion (Figure 1) certainly occurs at room temperature, and experimental estimates of the inversion barrier have been obtained by studying the racemization of substituted benzene oxides.[25,26] Although it is unclear how substituents might affect the energy of this barrier, an experimental barrier of 27.2 kJ mol^{-1} was estimated at 135 K for 2-cyanooxepin and 2-(ethoxycarbonyl)-7-ethyloxepin.[25] The geometry of the transition state for the inversion of simple oxepin **4** is its planar form. The free energy of activation of this process with **4** is calculated from our QCISD(T) data to be 19.0 kJ mol^{-1} at 298 K. This is a significantly higher barrier than an earlier estimate of 6.3 kJ mol^{-1} at HF/6-31G*//HF/STO-3G.[5c]

In the planar form of dimethyloxepin **10**, there are two possible C_{2v} structures, one with the methyls' hydrogens eclipsing the annular oxygen, and the other in which methyls' hydrogens are staggered with respect to the oxygen. Every basis set predicted that the latter is preferred, consistent with a differential hyperconjugation argument (*i.e.*, $\sigma_{CH} \rightarrow \sigma^*_{CO} > \sigma_{CH} \rightarrow \sigma^*_{CC}$). The QCISD(T) $\Delta G^‡$ for inversion with **10** is 25.1 kJ mol^{-1}, about 6 kJ mol^{-1} higher than that of **4** at all post-Hartree−Fock levels, indicating that this pattern of substitution only modestly increases the barrier to inversion.

The $\Delta G^‡$ for the inversion of thiepin **6** (35.0 kJ mol^{-1} with QCISD(T)) is almost twice that for oxepin **4**. Two reasons for this may be greater antiaromatic destabilization and greater ring strain in **6**. The planar forms have shorter double bonds and longer single bonds than those of the corresponding preferred boat conformers (Table 2), and this effect is greater in planar thiepin than in planar oxepin. The greatest shortening observed is only on the order of 0.01 Å. On the other hand, some bond angles undergo a change of 10° or more on going from the boat conformer to the planar form. This suggests that the inversion barrier is mainly due to an increase in ring strain in the planar form.

F. Barriers to Tautomerization. Vogel and Günther[4] experimentally determined the $\Delta H^‡$ for the isomerization of **3** to **4** to be 36.8 kJ mol^{-1}, and Jennings and co-workers[26] measured $\Delta H^‡$ to be 36.0 kJ mol^{-1} with a chiral, monosubstituted system. As can be seen in Table 1, the addition of correlation energy very significantly decreases the computed electronic activation energies. At QCISD(T), we estimate the enthalpy of activation to be 29.38 kJ mol^{-1}. The dimethyl analog gave a similar value for this barrier (32.88 kJ mol^{-1}).

On the other hand, for the benzene sulfide−thiepin system, we can predict that the rate of valence tautomerization will be much slower than that in the oxygen system, as the enthalpy of activation for **5** → **6** is 85.69 kJ mol^{-1}.

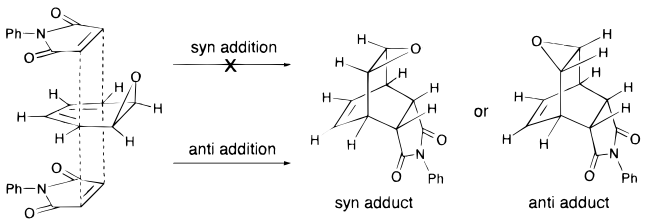
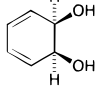


Figure 3. Facial selectivity in the Diels−Alder reaction of **3** with *N*-phenylmaleimide.

G. Effects of Protonation on 3 and 4. In order to model the effect of an acid on the valence tautomerism of **3** and **4**, we calculated the structures and energies of the oxygen-protonated species. For **3** and the transition state of tautomerization, two protonated isomers of C_S symmetry are possible: the added hydrogen can be either *exo* or *endo* with respect to the diene moiety. For **4**, there is only one protonated isomer, because the hydrogen is nearly planar with the COC moiety. The *endo* structures are lower in energy, consistent with a simple rationalization *via* differential hyperconjugative stabilization (*i.e.*, $n \rightarrow \sigma^*_{CC} > n \rightarrow \sigma^*_{CH}$). In a recent paper, Glusker and co-workers[27] claim that the *O*-protonated benzene oxide is a transition state and not a minimum. Our calculations show otherwise. Glusker only calculated the *exo* isomer using HF/6-31G. We calculated the *exo* isomer to be less stable than the *endo* isomer by 10.91 kJ mol^{-1} at HF/6-31G*. It is well-known that split-valence sp basis sets without polarization functions cannot properly predict the pyramidality of heteroatoms.[28]

Protonation stabilizes **3** more than **4** by 40.2 kJ mol^{-1} at the MP2/6-31G*//MP2/6-31G* level. The pronounced effect on the position of equilibrium has important implications, since in the presence of acid, **3** reacts to give phenol, probably *via* protonation of the oxide form, followed by aromatization.[27]

H. Facial Selectivity in the Diels−Alder Reaction of Benzene Oxide 3. In **3** the position of the oxygen relative to the diene is similar to that in 1,3-cyclopentadienes substituted in the 5-position by an oxygen function. Such cyclopentadiene derivatives undergo Diels−Alder reactions exclusively on their faces *syn* to the oxygen atoms.[29] However, Diels−Alder reactions of **3** with *N*-phenylmaleimide and with dimethyl acetylenedicarboxylate also provide single adducts, but these are the products of addition to the face of the diene *anti* to the oxygen (Figure 3).[10] This difference is not due to the fact that **3** contains a cyclohexadiene system because *N*-phenylmaleimide also adds very predominantly to the face of **13** *syn* to its oxygens.[30]



13

Ethene and ethyne served as simple model dienophiles in our computational examination of facial selectivity in the Diels−Alder reactions of **3**. The structures of the transition states on both faces of **3** along with the corresponding products have been calculated at the HF/6-31G* level. The *syn* and *anti* transition states have an isodesmic relationship, as do the two products of these transition states, therefore the computational shortcomings of this lower level of theory are largely obviated[31] and the experimental results of the reactions are predicted accurately. With ethene, the activation barrier for *syn* addition (212.5 kJ

mol^{-1}) is much higher than that for the corresponding *anti* addition (174.2 kJ mol^{-1}). The same is true for ethyne (*syn* addition, 241.4 kJ mol^{-1}, and *anti* addition, 188.0 kJ mol^{-1}). However, the product of *syn* addition is slightly more stable than the product of *anti* addition (ΔHs −107.3 *versus* −103.1 kJ mol^{-1}, respectively, with ethene), which rules out any product-development control in the facial selectivity.

In our preliminary examination of the cyclopentadienes we had partitioned the influences on facial selectivity by determining the energies of the diene and the dienophile in their transition state geometries, *i.e.*,

$$\Delta E_{\text{act}} = \Delta E_{\text{diene deformation}} + \Delta E_{\text{dienophile deformation}} + \Delta E_{\text{interaction}}$$

This led to the demonstration that the facial selectivity was largely due to the "deformation energy" of the diene moiety in the transition state.[31] This partitioning process was carried out with the transition states for *syn* and *anti* addition of **3** using ethene as the dienophile. The deformation energies of the diene moieties (145.2 and 101.3 kJ mol^{-1}, *syn versus anti*) are greater than either the deformation energies of the dienophile moieties (44.0 and 54.8 kJ mol, *syn versus anti*) or the diene−dienophile interaction energies (23.4 and 18.2 kJ mol^{-1}, *syn versus anti*), consistent with the major factor determining the facial selectivity being the deformation of the diene.

An examination of the geometry of the oxirane ring of **3** as it proceeds to the *syn* and *anti* transition states reveals that much larger changes occur on going to the unfavored, *syn* transition state. For example, the length of the oxirane's carbon−carbon bond shortens by 0.033 Å in the *syn* transition state, but only by 0.012 Å in the *anti* transition state. In addition, higher torsional forces in the *syn* transition state are clearly reflected in changes of the dihedral angles: C-2−C-1−C-4−C-5 decreases by 42.9° for *syn versus* 28.4° for *anti*, and C-1−C-6−C-5−O increases by 7.4° for *syn* but only 2.6° for *anti*. These differences in geometry are consistent with a strong steric interaction leading to deformation of the oxirane system in the *syn* transition state. This effect is large since the oxirane ring is almost perpendicular to the plane of the cyclohexadiene ring in **3**, whereas the hydrogens on the *anti* face are nearly coplanar with the cyclohexadiene moiety, as would be the two methyl groups of **9** or the three-carbon bridge of **11**, both of which also add dienophiles exclusively *anti* to the oxygen.[30]

Conclusions

The MP4 and the QCISD(T) data generally provide similar enthalpies and activation barriers, *i.e.*, within 4 kJ mol^{-1} of each other, for these valence tautomeric systems. Substitution by methyl groups at positions 2 and 7 (oxepin numbering) destabilizes the bicyclic form **9** relative to the oxepin **10**, whereas replacement of the oxygen with sulfur both stabilizes the bicyclic form **5** and destabilizes the monocyclic thiepin **6**, relative to **3** and **4**. Barriers to tautomerization and inversion are higher in the sulfur system. The calculated orbital energies agree linearly with the ionization energies derived from photoelectron spectra and allow correct assignments to be made. Protonation of **3** and **4** results in a stabilization of the bicyclic form relative to the monocyclic tautomer. Strong steric interactions in the *syn* transition state are responsible for the facial selectivity in the Diels−Alder reactions of **3**.

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Supporting Information Available: Optimized geometries at several levels in the form of compressed MUNGAUSS Z-matrices, tables of vibrational frequencies as calculated from GAMESS and Gaussian 92, and tables of total energies including some SCRF results (37 pages). Ordering information is given on any current masthead page.

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(22) Vogel showed that the proportions of **3** and **4** in solution show a marked dependence on the polarity of the solvent.[3] We used self-consistent reaction field theory (SCRFT) to probe solvent effects computationally.[23] Our model was crude in that we assumed a spherical cavity of the same size for all species. Furthermore, SCRFT does not consider hydrogen bonding between a protic solvent and the solute, which could be a major contributor to the **3**−**4** equilibrium.[24] Nevertheless, our results are qualitatively consistent with experiment. As ϵ increases, the amount of stabilization afforded by the solvent is directly proportional to the dipole moment of the species under consideration. (At HF/6-31G**//HF/3-21G, the dipole moment of **3** is 2.63 and the dipole moment of **4** is 1.40.) A reasonable estimate for the radius (r) of the cavity is 5.0 Å. Using the same solvents as Vogel employed in his NMR work[3] and applying these to

$$k = \frac{2(\epsilon - 1)\,1}{2\epsilon + 1r^3}$$

one obtains $k = 0.000\ 46$ bohr^{-3} for isooctane ($\epsilon = 1.95$) and $k = 0.001\ 16$ bohr^{-3} for 85:15 water−methanol ($\epsilon = 72$ by interpolation between the dielectric constants of water and methanol) giving a change of $0.000\ 70$ bohr^{-3} and a resulting difference in the enthalpies of 1.7 kJ mol^{-1}. An experimental difference in ΔG between the two solvents of 7.6 kJ mol^{-1} can be determined from Vogel's data. Given the lack of sophistication in our model, the uncertainty in Vogel's UV data with regard to the extinction coefficient assumption, and the likelihood of a significant entropy term in ΔG, the computed result is not unreasonable.

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