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CBS-QB3 computational examination of substituent effects on the interconversion of 1,3,5-cyclooctatriene and bicyclo[4.2.0]-2,4-octadiene

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Abstract

The position of equilibrium between 7-substituted and 7,8-disubstituted 1,3,5-cyclooctatrienes (**1**) and the corresponding valence isomeric bicyclo[4.2.0]-2,4-octadienes (**2**) is highly sensitive to the nature of substituents. In particular, the difference between trans and cis-7,8 isomers in this regard has never been explained. These differences have been clarified by computational means. The CBS-QB3 hybrid quantum chemical computational method reproduces the experimental free energy differences between a series of cyclooctatrienes (**1**) and the corresponding valence isomers (**2**) with excellent accuracy; the MAD and root mean square (rms) differences are 0.54 kcal/mol and 0.58 kcal/mol, respectively. The energy barriers between several derivatives of **1** and **2** were computed with good accuracy (MAD=1.3 kcal/mol and rms=1.5 kcal/mol) by the same procedure. The dihedral angle between the substituents *increases* upon electrocyclic conversion of trans-7,8-disubstituted cyclooctatrienes to the bicyclic isomer and *decreases* for the corresponding cis isomers. This differential effect explains both the higher bicyclic proportion at equilibrium and the faster rate of cyclization in the trans series compared to cis.

1. Introduction

In the course of a recent study on the anodic electrochemical oxidation of cyclooctatetraene in methanol,[1] we became aware of the surprisingly large effects of substituents in the system consisting of 1,3,5-cyclooctatriene and its valence tautomer bicyclo[4.2.0]-2,4-octadiene. Huisgen et al. examined the kinetic barriers to conversion of a series of 7-substituted and 7,8-disubstituted cyclooctatrienes (**1**) into the corresponding bicyclooctadienes (**2**) as well as the position of equilibrium between the two isomers (Eq. 1).[2] The equilibrium between **1** and **2** was found to be highly dependent upon the nature of X and Y, as is the activation barrier for the conversion of **1** to **2**. In view of projected synthetic experiments in this area, we became interested in the possibility of using computational methods to predict such data for unknown substituents. We report here the results of such a study. The CBS-QB3 computational procedure of Petersson et al.[3] was chosen for its rather high accuracy combined with relative speed compared with some other popular computational techniques. The CBS-QB3 method has been widely used for accurate computation of energies of small organic systems. Houk et al. in fact used CBS-QB3 energies as the benchmark to compare the accuracy of reaction enthalpies and enthalpies of activation of a variety of pericyclic and 1,3-dipolar cycloadditions computed by a number of computational techniques.[4]

1 **2**

a, XY = CH_2CO
b, XY = CH_2CH_2
c, XY = CH_2CHBr
d, XY = CH_2CHOAc
e, XY = *cis*-CHClCHCl
f, XY = *cis*-CHMeCHMe
g, XY = *trans*-CHMeCHMe
h, XY = *trans*-CHClCHCl

(1)

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Table 1
Comparison of experimental and computed values for the free energy of electrocyclization of substances **1**–**2**

X–Y	ΔG_{exptl}[a] (kcal/mol)	$\Delta G_{\text{CBS-QB3}}$[b] (kcal/mol)	Error[c] (kcal/mol)	ΔG_{B3LYP}[d] (kcal/mol)	Error[c] (kcal/mol)
CH_2CO	1.75	1.64	−0.11	4.66	+2.91
CH_2CH_2[e]	1.40	0.81	−0.59	1.60	+0.2
CH_2CHBr	0.41	−0.06	−0.47	1.20	+0.79
CH_2CHOAc	−0.08	−0.72	−0.64	−1.09	−1.01
cis-di-Cl	−0.92	−1.26	−0.34	−1.25	−0.33
cis-di-Me	−0.96	−1.72	−0.76	−1.66	−0.70
trans-di-Me	−1.82	−2.67	−0.85	−3.16	−1.34
trans-di-Cl[f]	−3.04	−3.58	−0.54	−3.56	−0.52

[a] Free energy change for the conversion of **1** to **2**, measured at 60 °C unless noted from the reported ratio of **1** to **2**.
[b] Free energy change computed by the CBS-QB3 method.
[c] $\Delta G_{\text{computed}} - \Delta G_{\text{exptl}}$.
[d] Free energy change computed by the density functional B3LYP/6-31G(d) method.
[e] Measurement and computation at 100 °C.
[f] Measurement and computation at −30 °C.

Table 2
Comparison of experimental and computed values for the free energy of activation for electrocyclization of **1** to**2**

X–Y	ΔG_{exptl}[a] (kcal/mol)	$\Delta G_{\text{CBS-QB3}}$ (kcal/mol)	Error[b] (kcal/mol)	$\Delta G^{*}_{\text{B3LYP}}$ (kcal/mol)	Error[b] (kcal/mol)
CH_2CO	23.3	24.9	+1.6	24.5	+1.2
CH_2CHOAc	24.0	25.2	+1.2	23.8	−0.2
CH_2CHBr	24.3	24.3	+0.0	26.7	+2.4
cis-di-Cl	24.4	25.7	+1.3	24.1	−0.3
CH_2CH_2	26.9	28.2	−2.3	26.8	−0.1
trans-di-Me	—[c]	21.4	—	21.7	—
trans-di-Cl	—[c]	19.3	—	19.3	—

[a] Computed from the reported ratios of **1** to **2**.
[b] $\Delta G_{\text{computed}} - \Delta G_{\text{exptl}}$.
[c] Not measured.

2. Results and discussion

From Table 1, it can be seen that the CBS-QB3 method reproduces the free energy differences between isomers **1** and **2** (ΔG for Eq. 1) with excellent accuracy; the MAD and root mean square (rms) differences are 0.54 kcal/mol and 0.58 kcal/mol, respectively. The fact that the MAD is actually better than that (1.1 kcal/mol) of the CBS-QB3 method itself[3] is unsurprising, in view of the small sample size in the present work and, more likely, the fact that the ΔG values are the difference between the CBS-QB3 computations on the isomers **1** and **2**, permitting inaccuracies in the method to cancel out. Presumably this also accounts for better accuracy of the B3LYP/6-31G(d) computations (MAD of 0.98 and rms difference of 1.27) compared with the much poorer intrinsic accuracy (MAD=7.9 kcal/mol) of this method.[7] Nevertheless, the CBS-QB3 method is clearly superior, with every computed value of ΔG agreeing with experiment within 1 kcal/mol. For each substituent, Eq. 1 is predicted by the CBS-QB3 procedure to be more exothermic (or less endothermic) than the experimental value. No such trend is apparent in the B3LYP/6-31G* computations. These results give the confidence that one can use the computed geometries to interpret the conformational and kinetic preferences for the conversion of **1** to **2**.

Since Huisgen had also reported activation parameters for conversion of several substituted cyclooctatrienes to the corresponding bicyclooctadienes ($\mathbf{1} \rightarrow \mathbf{2}$), it was of further interest to determine how well the activation barrier might be computed using these methods. The results are shown in Table 2 for the derivatives studied by Huisgen et al. As one might expect, this computation is more challenging, though the MAD is still only 1.3 kcal/mol. In this case, the density functional computation produces barriers slightly more accurately (MAD=0.8 kcal/mol).

The possible reasons for the large substituent effects exhibited in this system are of interest. Huisgen suggested two possibilities, the first being that this might arise by stabilization of the bicyclic tautomer through increased s-character in the bond between the ring and the substituent, an effect more notable in small rings.[2] However, as Huisgen et al. recognized, it seems very unlikely that this effect could be large enough to account for the observed effects. As a matter of fact, the hybridization at C-7 in bicyclo[4.2.0]-2,4-octadiene (**2b**) is no different to that in cyclooctane, as measured by the size of the one-bond $^{1}H-^{13}C$ NMR coupling constants.[2] Another possibility advanced by Huisgen et al. to account for the experimental results does seems to be a significant contributor. They suggested that 'the increase in bond angles [presumably, dihedral angles] in the four-membered ring should reduce conformational strain'. They concluded, however, that this effect is unlikely because 'the higher bicyclic proportion with trans-7,8-disubstitution [**1g** and **1h**], compared with the cis-compounds [**1e** and **1f**], contradicts the expectation for the relief of conformational strain [upon cyclization]'. Actually, however, our Hartree–Fock geometrical optimization computations do support an interpretation based on conformational effects. Their latter comment appears to rest upon the assumption that the substituents are farther apart in both *cis*-**2** and *trans*-**2** than in **1**. However, the dihedral angles between the 7,8 substituents in **1e**–**h** and **2e**–**h** exhibit a consistent pattern (Table 3). The dihedral angles between the substituents are very similar in the cyclooctatriene system **1** for both the cis and trans isomers. Upon going from the cyclooctatriene to the bicyclic structure, the dihedral angle between the methyl or chlorine substituents in the trans isomers does increase by ca. 30°–40°, i.e., the substituents move away from each other, presumably relieving strain. In the cis series, on the other hand, the opposite takes place, with the dihedral angles *decreasing* by ca. 35°–40°, so that the substituents approach each other more closely. The relief of non-bonded strain would then account for the increased

Table 3
Dihedral angles between substituents in 7,8-disubstituted derivatives measured from the B3LYP/6-31G(d) optimized structures

Substituents	Dihedral angle in **1** (°)	Dihedral angle in **2** (°)
cis-di-Cl	62	28
cis-di-Me	70	24
trans-di-Cl	70	101
trans-di-Me	56	99

proportion of **2** at equilibrium for the trans isomers. The increased proportion of bicyclic isomer in the trans-dichloro series compared to the trans-dimethyl series probably arises from the same phenomenon, possibly unfavorable induced bond dipoles in the *anti* conformation of the dichloride,[9] that gives rise to an increased proportion of *gauche* conformation in 1,2-dichloroethane compared to butane. It is not possible to make a corresponding statement concerning substituent effects on the activation barriers because kinetic data were not reported for the trans isomers **1g** and **1h**, but a similar effect must be operating, since the computed value for the barrier energy for **1h** is lower than that for the cis isomer **1e** and the barriers for cyclization of **1g** and **1h** are computed to be lower than that for any of the other derivatives studied kinetically. These facts are consistent with the trends observed by Huisgen et al.[2] The effects of solvation were not included in these computations. It is likely that, like many electrocyclic reactions, these conversions are insensitive to such effects.

3. Computational method

These substances, particularly **1d** and **2d**, exhibit one or more local conformational minima. For this reason, the global minimum energy conformation was located for each compound by a preliminary search involving several hundred starting conformations.[5] In general two enantiomeric conformations were found for each disubstituted cyclooctatriene and for the parent triene. No low-lying conformations within 3 kcal/mol of these were found. The energy of the global minimum conformation was then computed at the density functional B3LYP/6-31G(d) level, with full geometry optimization, using the Gaussian '03 suite of programs.[6] The energy of each such optimized geometry was then computed at the CBS-QB3 level.[3] Strictly speaking, a second optimization following the molecular mechanics global search is unnecessary because the first step in the CBS-QB3 computation is also a geometrical optimization, [3a] but it was convenient to use the output file of the B3LYP computation as input into the CBS-QB3 run. Computations on the transition states omitted this first step because otherwise the final geometry was that of one of the ground state isomers. Petersson et al. have shown that energies computed by the CBS-QB3 method have a mean absolute deviation (MAD) of 1.1 kcal/mol, whereas those computed by B3LYP/6-31G* have an MAD of 7.9 kcal/mol.[7] The computed values of ΔG at both of these computational levels, together with the experimental values,[2] are presented in Table 1. The energy barrier to conversion of **1** to **2** was also computed for each substance as follows. The transition state between **1** and **2** was located by applying Schlegel's synchronous-transit-guided quasi-Newton method[8] as implemented (QST2) in Gaussian '03 to the B3LYP-6-31G(d) computed energies of **1** and **2** for each substituent. The energy of the resulting transition state geometry for **1**–**2** pair was then computed at the CBS-QB3 level to obtain the respective activation barrier (Table 2). The dihedral angle between the two substituents in each of the 7,8-disubstituted derivatives **1e**–**h** and **2e**–**h** was measured from the B3LYP/6-31G(d) optimized structure (Table 3). All compounds **1** and **2** were identified as exhibiting zero imaginary frequencies. All transition states exhibited one imaginary frequency.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.12.041.

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