

The 16 kcal/mol Anomaly: Alteration of [2 + 2 + 2] Cycloaddition Rates by Through-Bond Interactions

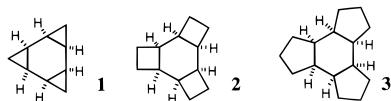
Dorota Sawicka, Sarah Wilsey, and K. N. Houk*

Department of Chemistry and Biochemistry
University of California
Los Angeles, California 90095-1569

Received December 22, 1997

Revised Manuscript Received November 21, 1998

The [2 + 2 + 2] retro-cycloaddition reactions of bridged cyclohexanes show an enormous acceleration of cleavage of cyclopropane-bridged systems compared to cyclobutane-bridged systems.¹ The reactions of simple derivatives of **1** occur readily at 60 °C; **1** has an estimated activation energy of about 25 kcal/mol.¹ The ring-opening reaction of **2** is only 7 kcal/mol less



exothermic but only occurs above 400 °C, with an activation energy of over 50 kcal/mol.²

The patterns found for this and other³ systems show a general preference for cleavage of odd-membered rings. An anomalously high rate of cyclopropane cleavage has also been noted by Ingold and Beckwith in several radical systems⁴ and by Stirling and co-workers in anionic systems.^{5,6} Semiempirical^{5,6} and ab initio⁷ calculations led these authors to the conclusion that the strain energy in cyclopropane is released more efficiently than in cyclobutane rings. Berson has suggested that orbital interactions involving bent bonds favor the [2 + 2 + 2] cycloreversion of 3,4-diazabicyclo[4.1.0]hept-3-enes over 3,4-diazabicyclo[4.2.0]oct-3-enes.⁸ We have found that symmetry-imposed differences in through-bond coupling can have very large effects on rate.

We investigated bond cleavage reactions in the [2 + 2 + 2] cycloreversions of systems **1**, **2**, **3** and related mono- and bis-substituted cyclohexanes using the hybrid density functional theory method, B3LYP, and the complete active space SCF methods, CASSCF. The 6-31G* basis set was used with both methods. All computations were carried out using GAUSSIAN 94.⁹ Reactants, transition structures, and products were fully optimized in each case. Frequency calculations were performed

(1) (a) Spielmann, W.; Fick, H.-H.; Meyer, L.-U.; de Meijere, A. *Tetrahedron Lett.* **1976**, *45*, 4057. (b) Rucker, C.; Müller-Böttcher, H.; Braschwitz, W.-D.; Prinzbach, H.; Reifensahl, U.; Irngartinger, H. *Liebigs Ann./Recueil* **1997**, 967. (c) Zipperer, B.; Müller, K.-H.; Gallenkamp, B.; Hildebrand, R.; Fletschinger, M.; Burger, D.; Pillat, M.; Hunkler, D.; Knothe, L.; Fritz, H.; Prinzbach, H. *Chem Ber.* **1988**, *121*, 757.

(2) Maas, M.; Lutterbeck, M.; Hunkler, D.; Prinzbach, H. *Tetrahedron Lett.* **1983**, *24*, 2143; Mohler, D. L.; Vollhardt, P. C.; Wolff, S. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1151.

(3) Wilsey, S.; Dowd, P.; Houk, K. N., to be submitted for publication.

(4) (a) Ingold, K. U.; Maillard, B.; Walton, J. C. *J. Chem. Soc., Perkin Trans. 2* **1981**, 970. (b) Beckwith, A. L. J.; Ingold, K. U. *Rearrangements in Ground and Excited States*; de Mayo, P., Ed.; Academic Press: New York, 1980; and references therein. For an example where stereoelectronic effects override this preference, see: Beckwith, A. L. J.; Moad, G. *J. Chem. Soc., Perkin Trans. 2* **1980**, 1083.

(5) (a) Stirling, C. J. M. *Tetrahedron* **1985**, *41*, 1613. (b) Stirling, C. J. M. *Pure and Appl. Chem.* **1984**, *56*, 1781 and references therein.

(6) (a) Earl, H. A.; Marshall, D. R.; Stirling, C. J. M. *J. Chem. Soc., Perkin Trans. 2* **1983**, 779. (b) Earl, H. A.; Stirling, C. J. M. *J. Chem. Soc., Perkin Trans. 2* **1987**, 1273. (c) Bury, A.; Earl, H. A.; Stirling, C. J. M. *J. Chem. Soc., Perkin Trans. 2* **1987**, 1281.

(7) Tonachini, G.; Bernardi, F.; Schlegel, H. B.; Stirling, C. J. M. *J. Chem. Soc., Perkin Trans. 2* **1988**, 705.

(8) Berson, J. A.; Olin, S. S.; Petrillo, E. W., Jr.; Pickart, P. *Tetrahedron* **1974**, *30*, 1639.

(9) GAUSSIAN 94 (Revision B2) Frisch, M. J. et al. Gaussian Inc., Pittsburgh, PA, 1995.

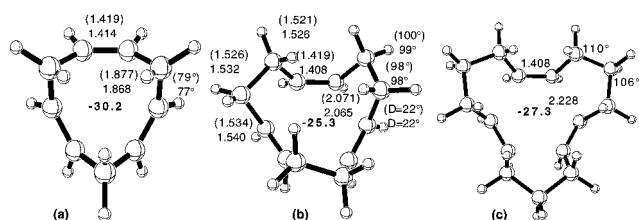


Figure 1. B3LYP/6-31G* and (CASSCF) optimized geometries of the transition structures for [2 + 2 + 2] cycloreversion reactions of cyclohexanes bridged by three (a) cyclopropane, (b) cyclobutane and (c) cyclopentane rings.

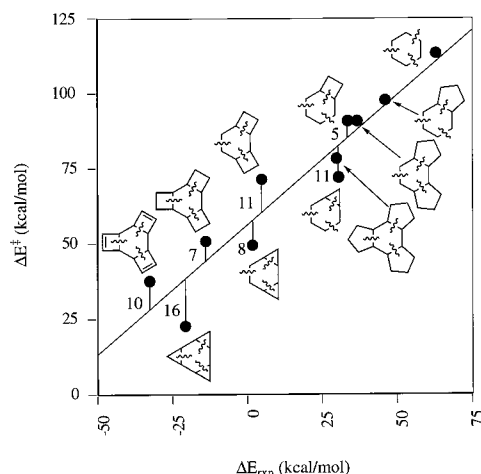


Figure 2. Plot of activation energy (ΔE^\ddagger) against energy of reaction (ΔE_{rxn}) for [2 + 2 + 2] cycloreversion reactions of unbridged and bridged cyclohexane systems. Deviations from the least-squares line are given next to the horizontal lines.

on all structures except the CASSCF transition structure for the cycloreversion of **2** due to computational expense. To assess the aromatic properties of the transition states, NICS (nucleus-independent chemical shift)¹⁰ values were calculated with GIAO-SCF/6-31G* on B3LYP/6-31G* geometries.

The transition structures for the [2 + 2 + 2] cycloreversions involving cyclohexanes bridged by three three-, four- and five-membered rings are shown in Figure 1.¹¹ The mono- and bis-bridged analogues of systems **1**, **2**, and **3** and the tris-cyclobutenacyclohexane were also studied. These reactions are all essentially synchronous concerted processes. The ΔE_{rxn} are plotted against ΔE^\ddagger for all cases (Figure 2 and Table 1). CASSCF values for several systems give the same relative activation energies. The activation energy is related to the energy of reaction by $\Delta E^\ddagger = 0.86\Delta E_{\text{rxn}} + 55.8$: the more exothermic the reaction, the lower the activation energy. Deviations below this line indicate that the activation energy is anomalously low for that energy of reaction. Deviations above the line suggest that the transition state is less stable than expected from the energy of reaction. The parent reaction and those involving cleavage of five-membered rings lie within a few kcal/mol of the least-squares line. The mono-, bis-, and tris-cyclobutenacyclohexanes and tris-cyclobutenacyclohexane lie above the line, with deviations corresponding to activation energies 5–11 kcal/mol higher than expected. The mono-, bis-, and tris-cyclopropacyclohexanes lie below the line;

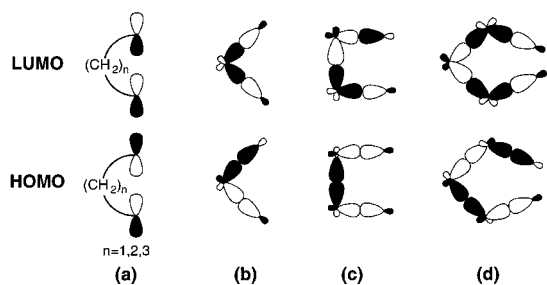
(10) (a) Schleyer, P. v. R.; Maerker, C.; Dransfeld, A.; Jiao, H.; Hommes, N. J. R. v. E. *J. Am. Chem. Soc.* **1996**, *118*, 6317. (b) Jiao, H. and Schleyer, P. v. R., submitted for publication.

(11) The [2 + 2 + 2] cycloreversion of **1** has been calculated using MINDO/3, see: Spanget-Larsen J.; Gleiter, R. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 441.

Table 1. B3LYP/6-31G* Zero Point Corrected Activation Energies and Energies of Reaction for [2 + 2] Cycloreversion Reactions of Bridged and Unbridged Cyclohexanes^a

System	ΔE^\ddagger /kcal/mol	ΔE_{rxn} /kcal/mol	System	ΔE^\ddagger /kcal/mol	ΔE_{rxn} /kcal/mol
	112.8 (115.6)	63.1 (33.6)		50.4 (59.2)*	-13.9 (-32.4)*
	71.7	30.8		37.3	-32.8
	49.1	1.95		97.1	46.6
	22.0 (26.1)	-20.8 (-44.2)		90.4	37.0
	90.1	34.0		78.0	29.7
	70.9	5.04			

^a CASSCF values are given in parentheses. *Not zero-point energy corrected

**Figure 3.** Schematic representation of HOMO and LUMO of (a) a cleaving σ bond in the transition state, (b) trimethylene, (c) tetramethylene, and (d) pentamethylene groups.

these transition structures are up to 16 kcal/mol lower in energy than expected. The activation energies for cleavage of the three-membered ring systems are 18–28 kcal/mol lower than the respective four-membered systems.

The anomalously rapid cleavage of three-membered rings and slow cleavage of four-membered rings can be explained in terms of through-bond interactions involving the cleaving σ bond and attached groups. Figure 3 shows the HOMO and LUMO of a breaking σ bond (a), along with the simple C-approximation¹² σ orbitals of trimethylene (b), tetramethylene (c), and pentamethylene (d) chains. The highest occupied σ molecular orbital (HO- σ -MO) of the fragments joining the breaking bond in the four-membered ring is symmetric and therefore mixes with the symmetric σ orbital of the breaking bond. Both of these orbitals are doubly occupied, and this four-electron interaction is destabilizing and raises the activation energy. The HO- σ -MOs of three- and five-membered rings are antisymmetric, and are, therefore, of the wrong symmetry to mix with the σ orbital of the breaking bond. No destabilizing interactions are present, but the trimethylene and pentamethylene σ orbitals are of the correct symmetry to mix with the σ^* orbitals of the breaking bond, leading to stabilization. Additional stabilizing interactions will arise from mixing of the symmetric lowest unoccupied σ^* molecular orbitals (LU- σ -MOs) with the σ orbitals of the breaking bond. These stabilizing two-electron interactions are very strong for three-membered rings, but become almost negligible for five-membered rings due to poor overlap of the σ -orbitals with the breaking bond orbitals. Haddon used similar orbital interaction arguments to explain the preference of a cyclopropane unit over a cyclobutane unit as a homoaromatic linkage.¹³

Further evidence for these orbital interactions comes from NICS values, which are an effective probe of aromaticity in transition

(12) Sandorfy, C.; Daudel, R. *C. R. Acad. Sci. Ser. C* **1954**, 238, 93.

(13) (a) Haddon, R. C. *Tetrahedron Lett.* **1974**, 33, 2797. (b) Haddon, R. C. *Tetrahedron Lett.* **1974**, 49–50, 4303.

states of pericyclic reactions.¹⁰ Aromatic molecules such as benzene have large negative NICS values (–11.5), and aromatic transition states have NICS values of around –25.¹⁰ Antiaromatic molecules such as cyclobutadiene have positive NICS values (28.8), and nonaromatic molecules have NICS values close to zero.¹⁰ NICS values were computed at the centers of the cyclohexane ring and fused rings in the reactants and transition structures. The NICS values at the center of the cyclohexane ring in the transition state (Figure 1) for all of the systems shown have large negative values typical of highly aromatic transition states. The tris-cyclobutacyclohexane, **2**, has the least aromatic transition state of the four systems, due to the antiaromaticity of the cleaving four-membered rings. The NICS values in the small rings of the transition structures, show that there is a small, but positive, NICS value in the cleaving cyclobutane ring (+2.5). The center of the cyclopropane and cyclopentane ring has a negative NICS values in the transition structures (–39.4), reflective of stabilizing aromatic interactions, while the effect has nearly vanished in the cleaving cyclopentane (–4.4).¹⁴

In 1980, Verhoeven suggested that the orbital interactions through-bonds (OITB), studied earlier by Hoffmann,^{15,16} could influence the rates of bond formation in bifunctional carbon chains, intramolecular hydrogen and hydride transfer, and radical–olefin cyclizations.¹⁷ The latter had previously been classified according to Baldwin's rules based on stereochemical factors.¹⁸ However, experimental evidence for such interactions has been sparse. Spectroscopic detection of the nondegeneracy of ionization potentials in large symmetric unsaturated cyclic systems^{16a,16b,19} provides strong evidence for OITB, but the chemical consequences of OITB have proven elusive. The heterolytic Grob fragmentation^{16c,20} and the Birch reductions of Paddon-Row and Hartcher²¹ and the carbanion cyclizations of Stirling²² are among very few examples that have appeared in the literature. Thus, the significance of OITB in chemical reactivity is normally assumed to be quite small. We have discovered reactions in which OITB lead to significant rate enhancements of ring cleavage in three-membered rings, relative to the norm, and rate decelerations involving four-membered ring cleavage. OITB in the transition states cause each of them to deviate from expectation by as much as 16 kcal/mol! OITB should operate in bond-cleavage reactions of all small ring systems and can account for the large rate enhancements observed in three-membered rings relative to four-membered rings in many different radical, anionic, and neutral systems.^{1,2,4–6}

Acknowledgment. We are grateful to the National Science Foundation for financial support of this research and to the National Center for Supercomputing Applications, University of Illinois at Urbana-Champaign and the UCLA Office of Academic Computing for computational resources. S.W. thanks the Royal Society for a NATO Fellowship and the Fulbright Commission for a scholarship.

JA974322N

(14) The NICS value of –39 at the center of the small ring in the transition state of **1** may be inflated due to the close proximity of the C–C bonds. see Jiao, H.; Nagelkerke, R.; Kurtz, H. A.; Vaughan Williams, R.; Borden, W. T.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1997**, 119, 5921.

(15) Hoffmann, R.; Imamura, A.; Hehre, W. J. *Am. Chem. Soc.* **1968**, 90, 1499.

(16) (a) Heilbronner, E.; Schwesinger, A. *Helv. Chim. Acta* **1975**, 58, 936. (b) Martin, H. D.; Schwesinger, A. *Chem. Ber.* **1974**, 107, 3143. (c) Gleiter, R.; Stohrer, W. D.; Hoffmann, R. *Helv. Chim. Acta* **1972**, 55, 893. (d) Kawamura, T.; Matsunaga, M.; Yonezawa, T. *J. Am. Chem. Soc.* **1976**, 100, 92. (e) Brunck, T. K.; Weinhold, F. *J. Am. Chem. Soc.* **1976**, 98, 4392. (f) Lehn, J. M.; Wipff, G. *Tetrahedron Lett.* **1980**, 159.

(17) (a) Verhoeven, J. W. *Recl. Trav. Chim. Pays-Bas* **1980**, 99, 143. (b) Verhoeven, J. W. *Recl. Trav. Chim. Pays-Bas* **1980**, 99, 369.

(18) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.

(19) (a) Hoffmann, R. *Acc. Chem. Res.* **1971**, 4, 1. (b) Gleiter, R. *Angew. Chem., Int. Ed. Engl.* **1974**, 13, 696. (c) Pasman, P.; Verhoeven, J.; de Boer, Th. J. *Tetrahedron Lett.* **1977**, 207. (d) Cookson, R. C.; Henstock, J.; Hudec, J. *J. Am. Chem. Soc.* **1966**, 88, 1060.

(20) Grob, C. A. *Angew. Chem.* **1969**, 81, 343.

(21) (a) Paddon-Row: M. N.; Hartcher, R. *J. Am. Chem. Soc.* **1980**, 102, 662. (b) Paddon-Row: M. N.; Hartcher, R. *J. Am. Chem. Soc.* **1980**, 102, 671.

(22) Van der Kerk, S. M.; Verhoeven, J. W.; Stirling, C. J. M. *J. Chem. Soc., Perkin Trans. 2* **1985**, 1355.