

The Roles of Changes in Bonding vs. Packing Fraction in the Pressure-Induced Acceleration of the Diels-Alder Reaction¹⁾

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The rates of Diels-Alder reactions increase with pressure, giving rise to large negative activation volumes that are similar to reaction volumes. These negative volumes are generally ascribed to contraction occurring during bond formation, with the further inference that the reactions are concerted because the parity of $-\Delta V^*$ and $-\Delta V$ implies that both new bonds are forming in the transition state, rather than one bond at a time. We hold that this is difficult to reconcile with the Bell-Evans-Polanyi-Hammond postulate, and from calculations of intrinsic molar volumes we have reached different conclusions. (1) The intrinsic contraction arising from bond formation is very small. In the product it is only 11–16% of ΔV , and in the transition state, only 3–5% of ΔV^* . (2) Almost all the shrinkage in the system that occurs during reaction results from the loss of empty space surrounding the molecules, and not from the reaction itself. (3) Therefore the activation and reaction volume data are not useful as criteria of the Diels-Alder mechanism.

The effect of high pressure on reaction rates is a well-established tool in the investigation of mechanism^{2,3)}. If the transition state (TS) is smaller than the reactants, then the reaction is accelerated by pressure and ΔV^* is negative, while if the TS⁴⁾ is larger than the reactants, the reaction is pressure-retarded and ΔV^* is positive. One way the system can shrink on entering the TS is for bonds to form between atoms previously not bonded to each other, so that they approach bonding distance from the larger van der Waals distance. Such reactions are expected to be pressure-accelerated, and conversely for bond-breaking reactions. Another source of contraction leading to pressure-acceleration is the separation in the TS of electrostatic charge (as in, e.g., solvolysis), which gives rise to solvent electrostriction, a volume-decreasing event. This too can occur in the opposite direction and cause pressure-retardation.

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Die Bedeutung der Bindungsvorgänge gegenüber dem Packungsanteil bei der druckinduzierten Beschleunigung der Diels-Alder-Reaktion

Die Reaktionsgeschwindigkeit der Diels-Alder-Reaktion steigt mit zunehmendem Druck, begleitet von einem großen negativen Aktivierungsvolumen, das dem Reaktionsvolumen in etwa gleichläuft. Diese negativen Volumina werden meistens den während der Bindungsvorgänge auftretenden Kontraktionen zugeschrieben, wobei weiter angenommen wird, daß es sich um konzertierte Reaktionen handelt, da die Parität von $-\Delta V^*$ und $-\Delta V$ andeutet, daß die beiden neuen Bindungen im Übergangsstadium und nicht nacheinander gebildet werden. Unserer Meinung nach ist diese Annahme schwer mit dem Bell-Evans-Polanyi-Hammondschen Postulat zu vereinbaren. Unsere Berechnungen der inhärenten Molvolumina haben uns zu einer anderen Schlußfolgerung geführt. (1) Die auf die inhärenten Bindungsvorgänge zurückzuführende Kontraktion ist äußerst gering. Sie beträgt im Produkt nur 11–16% des ΔV und im Übergangszustand nur 3–5% des ΔV^* . (2) Fast die gesamte während des Reaktionsablaufs auftretende Volumentraktion ist auf Verlust an Leerraum um die Moleküle zurückzuführen und nicht auf die eigentliche Reaktion. (3) Aus diesem Grund sind Daten über Aktivierungs- und Reaktionsvolumina bedeutungslos für die Aufklärung des Diels-Alder-Reaktionsmechanismus.

Table 1. High pressure Diels-Alder reaction (diradical mechanism)

	ΔV^* [cm ³ /mol]	ΔV
Dimerization of isoprene ⁶⁾	–24.3	–45.5
Dimerization of cyclopentadiene (CPD) ⁵⁾	–20.0	–31.6
Free radical polymerization ²⁾	–22	

It has been known since 1939 that the Diels-Alder reaction is accelerated by pressure⁵⁾, as expected for a bond-forming process. Since its rate is generally not sensitive to solvent polarity, transient charge separation with concomitant solvent electrostriction is not expected to play a role. In the pioneering studies of Walling and co-workers (Table 1), it was found that $|\Delta V^*|$ was about half the volume of reaction $|\Delta V|$, leading them to propose that only one of the two new bonds existed in the TS, as would be the case if

there were a diradical intermediate⁶. With the advent of more sophisticated equipment, however, the preponderance of recent data have $|\Delta V^*|$ and $|\Delta V|$ about equal, so that the present climate of opinion holds that both new bonds are forming in the TS, i. e. that the reaction is concerted⁷⁻²⁰. Table 2 has some typical cases.

Table 2. High pressure Diels-Alder reaction (concerted mechanism)

Reaction	ΔV^* [cm ³ /mol]	ΔV
CPD + dimethyl acetylenedicarboxylate (ECCE) ⁷	-30.2	-33.9
Isoprene + acrylonitrile ¹³	-35.4	-37.0
2-Methoxybutadiene + MA ¹¹	-33.5	-31.9

We feel that there are inherent contradictions in both conclusions.

Diels-Alder, Diradical vs. Concerted

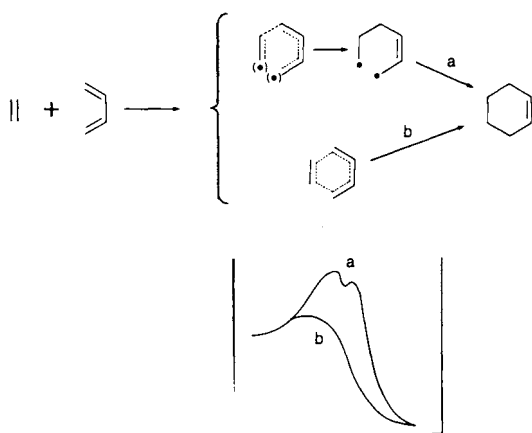


Figure 1 depicts the reaction coordinate (RC) for the two mechanisms. Since the diradical mechanism has a high-energy intermediate, the Bell-Evans-Polanyi-Hammond (BEPH)²¹ principle predicts a late TS closely resembling the diradical, with one of the two new bonds almost fully formed. The contraction in the TS then should be about one-half the total, as Walling said. In contrast, the concerted pathway has no intermediate, and since the reaction is highly exothermic, the BEPH principle predicts an early TS. Thus, although both new bonds form simultaneously (but not necessarily to the same extent) in the concerted TS²², bond formation is much less complete than in the diradical, so that one expects contraction in the TS to be *much less than in the product*²³, perhaps even less than half²⁴. We conclude that although Walling's early data support the diradical mechanism they do not exclude the concerted one, and that the recent data do not unambiguously support the concerted mechanism because they conflict with the BEPH principle.

There are other difficulties with the concerted interpretation. First, there are now many examples (Table 3) of

Diels-Alder (DA) reactions in which $|\Delta V^*| > |\Delta V|$ ², i. e. in which the TS appears to be smaller than the cycloadduct! Carried to its logical conclusion, this would mean that a partially formed bond can be smaller than a fully formed one. This anomaly can reach 10 cm³/mol, a significant fraction of a typical $|\Delta V^*|$. We believe this to be a physical impossibility. The phenomenon is not simply an artifact of the calculation, or due entirely to the experimental difficulty in obtaining accurate activation volumes, because at least one example is now known (Table 3) in which a retrodiene reaction, which goes in the volume-increasing direction, is pressure-accelerated.



Table 3. High pressure Diels-Alder reaction where $-\Delta V^*$ exceeds $-\Delta V$ (selected examples)

Reaction	ΔV^* [cm ³ /mol]	ΔV
Cyclohexadiene (CHD) + MA ⁷	-37.2	-30.3
1-Methoxybutadiene + MA ⁷	-45.4	-35.5
2-Methylfuran + acrylonitrile, retrodiene ²⁵	-1.0 to -3.4	

The problem has not gone unobserved²⁶. The most reasonable rationalization⁷ has been that secondary orbital interactions in the TS, i. e. transient bonding between atoms in the diene and dienophile that do not remain bonded to each other in the final product, produce transient shrinkage whose magnitude more than offsets the incompleteness in contraction during formation of the two permanent new bonds. Bearing in mind that a concerted cycloaddition must have an early TS²³, the interpenetration of interacting secondary orbitals must greatly exceed 10 cm³/mol.

If this were so, then there ought generally to be a difference of this magnitude in the volume requirements of *exo* vs. *endo* cycloadditions in those examples where secondary orbital interactions are possible. However, this is not observed²⁷. It is seen in Table 4 that such differences are of insignificant magnitude, and inconsistent in sign. Thus the anomaly remains unexplained.

Table 4. Can secondary orbital interactions explain $-\Delta V^* > -\Delta V$?

Reaction	$\Delta\Delta V^*$ <i>endo-exo</i> COOMe ²⁸ [cm ³ /mol]
CPD + methyl acrylate	-0.52
CPD + dimethyl maleate	-0.82
CPD + 	+0.21
CPD + 	+0.52

A second problem with the concerted interpretation concerns the relationship between ΔV^* and rate. Straightforward application of the BEPH principle leads to the expect-

tation that the faster the reaction, the earlier the TS on the RC⁴⁾ and consequently the smaller the amount of contraction. However, exactly the opposite is found. Table 5 shows a series of closely related cases in which in general $|\Delta V^*|$ increases with rate.

Table 5. High pressure Diels-Alder reaction (correlation between $-\Delta V^*$ and rate¹⁷⁾)

Reaction	Temp. [°C]	Rel. Rate	ΔV^* [cm ³ /mol]
2,3-Dimethyl butadiene + methyl acrylate	40	1.84	-30.2
2,3-DMB + butyl acrylate	40	2.14	-29.6
2,3-DMB + dimethyl fumarate	40	66.0	-32.9
Isoprene + MA	35	1680	-38.0
2,3-DMB + MA	30	3540	-41.3
1-Methoxybutadiene + MA	35	9340	-45.4

Furthermore, these three observations – that activation and reaction volumes are usually comparable; that sometimes $|\Delta V^*| > |\Delta V|$; and that $|\Delta V^*|$ increases with rate – conflict with not only the concerted but also the diradical mechanism.

All of the above-mentioned arguments that favor one or another mechanistic interpretation of the high-pressure data rest on the tacit assumption that ΔV^* and ΔV measure, at least significantly if not precisely, the contraction in the molecules that arises from bond formation. Is this assumption valid? We decided to test it by calculating the actual volumes of the molecules themselves (“intrinsic” volumes) before and after reaction. This “intrinsic molar volume” (IMV) refers to the volume of only the atoms and bonds of one mole of a given compound, as contrasted with “molar volume” (MV) which has the usual meaning of the volume, not only of the atoms and bonds, but also of the intervening space in the normal liquid state.

To obtain a standard figure for carbon-carbon single bond formation, we chose the simplest reaction first, the combination of two methyl radicals to form ethane. The π -bond radius was set equal to that of ethylene rather than methyl radical in order to get the closest approximation to the DA situation. The total intrinsic contraction in the system was found to be 3.6 cm³/mol, much less than typical $-\Delta V$'s per bond (15–20 cm³/mol) in DA reactions. Furthermore, this does not take into account the concomitant stretching of double into single bonds. When this is done, the intrinsic contraction for the overall cycloaddition is reduced from 7.2 to 4.0–5.4 cm³/mol (vide infra), which is only about 10–18% of typical $-\Delta V$'s. These results are set forth in Table 6.

Even smaller intrinsic contractions are found for TS's (Table 6). With a distance of 2.3 Å between reaction partners in a concerted TS³⁰⁾, the contraction for two methyls is reduced to 1.1 cm³/mol per bond, and the range of most DA cases (vide infra) to 1.2–1.6 cm³/mol for two bonds. This is only 3–6% of typical $-\Delta V^*$'s!³¹⁾ Clearly the magnitude of ΔV , and to an even greater extent ΔV^* , arises

principally from some source other than contraction during bond formation.

Table 6. The intrinsic contraction during bond formation [cm³/mol]

	$r = 2.3 \text{ \AA}$	$r = 1.54 \text{ \AA}$
2 CH ₃ → C ₂ H ₆ for 2 bonds	1.1 2.2	3.6 7.2
Typical Diels-Alder (2 bonds)	1.2–1.6	4.0–5.4
2 Propene → 1-Hexene		3.4 ²⁹⁾

Table 7. Effect of cyclization on density of hydrocarbons (20°C)³²⁾
 $n\text{-C}_x\text{H}_{2x+2}$ vs. $\text{cyclo}(\text{CH}_2)_x$

x	n	<i>cyclo</i>	<i>cyclo/n</i>
3	0.566 ^{a)}	0.677	1.20 (–30°C)
4	0.596 ^{a)}	0.720	1.21 (5°C)
5	0.626	0.746	1.19
6	0.660	0.779	1.18
7	0.684	0.810	1.18
8	0.703	0.835	1.19

^{a)} Interpolated.

If the intrinsic volume of reaction (ΔV) for DA's is only 4.0–5.4 cm³/mole, why are ΔV 's so large (–30 to –40 cm³/mol)? The reason is that cyclic molecules are generally more dense than acyclic ones. Typical data are presented in Table 7³²⁾, which shows that cyclization of simple hydrocarbons of chain length 3–8 gives rise to about 20% increase in density. The change in molecular formula during cyclization is not responsible for the increase in density because the density ratio is invariant with chain length. The IMV⁴⁾ of cyclohexane, 48.61 cm³/mol, is the same as that of the isomeric $n\text{-(CH}_2)_6$, 48.72 cm³/mol, showing that the greater density of cyclohexane does not result from any special property of its bonds. Instead, its source is the reduction during cyclization in the volume of *empty space* between the molecules (59 cm³/mol for cyclohexane). Cyclic molecules in general have higher packing fractions than acyclic ones.

In Table 8 are compared calculated intrinsic with experimental volumes and derived properties for almost all DA cases for which published data are complete enough to allow comparison. The increase in density attending cycloaddition is about right for the formation of one new ring. It is clear that ΔV 's consist principally (84–89%) of changes in empty space between the molecules^{33–37)}, and not in changes in molecular volumes occurring during reaction, because ΔV^* 's are only 11–16% of ΔV 's.

At the (concerted) TS, the intrinsic shrinkage vis-à-vis the experimentally derived ΔV^* is even more insignificant, with ΔV^* 's a mere 3–5% of ΔV^* 's. Thus of the apparent reduction in volume ΔV^* that takes place in the reactants as they proceed from the ground state to the TS, 95–98% represents something other than contraction of the system

Table 8. High pressure Diels-Alder reaction; comparison of intrinsic with experimental ΔV and ΔV^\ddagger [cm³/mol]

Compound	Solvent	MV	IMV	ES	ΔV	ΔV ES	ΔV	ΔV^\ddagger	ΔV^\ddagger	Ref.
CPD	EtOAc	81.4	36.1	45.3						
ECCE		119.9	60.1	59.8						
Cycloadduct		167.4	92.1	75.3	-4.1	-29.8	-33.9	-1.3	-30.2	9
CHD	CH ₂ Cl ₂	96.3	43.9	52.4						
MA		71.0	37.0	34.0						
Cycloadduct		137.0	76.5	60.5	-4.4	-25.9	-30.3	-1.3	-37.2	9
Piperylene	MeCN	98.4	41.1	57.3						
MA		69.8	37.0	32.8						
Cycloadduct		136.9	73.3	63.6	-4.8	-26.5	-31.3	-1.5	-43.1	13
Isoprene	n-BuBr	103.0	40.6	62.4						
Dimers		164.2	75.4	88.3	-5.3	-36.5	-41.9	-1.6	-34.5	16
Isoprene	Acetone	101.0	40.6	60.4						
MA		69.4	37.0	32.4						
Cycloadduct		134.5	73.7	61.4	-4.5	-31.4	-35.9	-1.4	-39.0	10
1-MeO-butadiene	n-BuCl	100.6	44.8	55.8						
MA		69.6	37.0	32.6						
Cycloadduct		134.7	77.8	56.9	-4.0	-31.5	-35.5	-1.2	-45.4	11
2-MeO-Butadiene	MeCN	101.3	45.6	55.7						
MA		69.8	37.0	32.8						
Cycloadduct		139.2	77.4	61.8	-5.2	-26.7	-31.9	-1.6	-33.5	13
Chloroprene	MeCN	93.0	42.3	50.7						
MA		69.8	37.0	32.8						
Cycloadduct		125.9	74.7	51.2	-4.6	-32.3	-36.9	-1.4	-41.6	13
2,3-DMB	n-BuCl		49.1							
MA			37.0							
Cycloadduct			81.3		-4.8	-31.5	-36.3	-1.5	-41.3	19
2,3-DMB	n-BuCl		49.1							
Me ₂ Fumarate			61.9							
Cycloadduct			106.5		-4.5	-32.7	-37.2	-1.4	-32.9	19
2,3-DMB	n-BuCl		49.1							
Me Acrylate			40.4							
Cycloadduct			84.2		-5.3	-31.7	-37.0	-1.6	-30.2	19
Isoprene	n-BuBr		40.6							
Acrylonitrile			27.8							
Cycloadduct			63.6		-4.8	-32.2	-37.0	-1.5	-33.1, -35.4	15
Isoprene	n-BuBr		40.6							
Me Acrylate			40.4							
Cycloadduct			75.9		-5.1	-31.8	-36.9	-1.6	-31.5, -30.8	15
Isoprene	n-BuBr		40.6							
MVK			36.6							
Cycloadduct			71.8		-5.4	-31.7	-37.1	-1.6	-36.9, -38.1	15
CPD	n-BuCl		36.1							
Me ₂ Fumarate			61.9							
Cycloadduct			93.8		-4.2	-32.5	-36.7	-1.3	-32.7	19
CPD	n-BuCl		36.1							
Me Acrylate			40.4							
Cycloadduct			71.8		-4.7	-31.0	-35.7	-1.4	-30.1	19
CPD	n-BuCl		36.1							
Dimer			67.4		-4.8	-28.2	-33.0	-1.5	-23.7	19
CPD-Cl ₄	n-BuCl		73.5							
Me Acrylate			40.4							
Cycloadduct			109.7		-4.2	-29.0	-33.2	-1.3	-24.6	19

during bond formation³⁸). Presumably this too is reduction of empty space.

If the reaction were concerted, a TS and its product would have the same shape except for the new bonds being slightly – and, as we have seen, negligibly from the standpoint of intrinsic volume – longer in the TS. However, the same can be said for a diradical, because only cyclo-diradicals go on to give product³⁹). Therefore, since bonding events account for merely 11–16% of ΔV 's and 3–5% of ΔV^* 's, we conclude that previous mechanistic conclusions favoring concert, which are based on comparison of bonding events in the TS and product as measured by ΔV and ΔV^* , must be reexamined. Neither the concerted nor the diradical mechanism for the DA reaction can be proven or disproven by high-pressure data at the present time.

*Method of calculation of molecular volume*⁴⁰): The method used to calculate the volume is based on a numerical integration using a nearly uniform distribution of points inside a sphere. The integration is done atom by atom using the following procedure. A unit sphere containing 1800 points is scaled to the size of the atom being considered and moved to be centered at the atomic center. Then for every atom which overlaps the atom in question, a plane is constructed perpendicular to the connecting line and which passes through the point of intersection of the two atomic surfaces. All points which lie on the side of the plane away from the atomic center are discarded. When this process is done the unique volume for this atom can be calculated as the product of the number of points remaining and the volume per point value obtained by dividing the original atom by 1800. This is repeated for all atoms in the structure and a final sum taken to obtain the overall volume.

van der Waals radii used were (in Ångströms): H, 1.00; C, 1.60; N, 1.40; O, 1.35; Cl, 1.75. Bond lengths were taken from Pople et al.⁴¹), with these in addition: C(sp³)–Cl, 1.77; C(sp²)–Cl, 1.71; C(sp)–Cl, 1.64. Bond angles (degrees): sp³, 109.47; sp², 120; sp, 180. Ring structures were built using the standard values and then minimized with MM2. Minimized structures were checked for closeness to standard values (except five-membered rings). In all cases where structures had symmetry, it was reflected in the bond lengths and angles.

¹) Presented at the Symposium on Diels-Alder Mechanisms, A.C.S. Meeting, Akron, Ohio, June 6, 1985.

²) T. Asano, W. J. le Noble, *Chem. Rev.* **78** (1978) 407.

³) W. J. le Noble, *Phys. Rev. Jpn.* **50** (1980) 207.

⁴) Glossary: TS, transition state; RC, reaction coordinate; BEPH, Bell-Evans-Polanyi-Hammond; DA, Diels-Alder; IMV, intrinsic molar volume; MV, molar volume; RDS, rate-determining step; ΔV , intrinsic volume of reaction; ΔV^* , intrinsic volume of activation; IMD, intrinsic molar density; ES, empty space; CPD, cyclopentadiene; ECCE, dimethyl acetylenedicarboxylate; MA, maleic anhydride; DMB, dimethylbutadiene; MVK, methyl vinyl ketone.

⁵) B. Raistrick, A. H. Sapiro, D. M. Newitt, *J. Chem. Soc.* **1939**, 1761.

⁶) C. Walling, J. Peisach, *J. Am. Chem. Soc.* **80** (1958) 5819. See also C. Walling, H. J. Schugar, *ibid.* **85** (1963) 607; C. Walling, D. D. Tanner, *ibid.*, 612.

⁷) R. A. Grieger, C. A. Eckert, *J. Am. Chem. Soc.* **92** (1970) 7149.

⁸) R. A. Grieger, C. A. Eckert, *Trans. Faraday Soc.* **66** (1970) 2579.

⁹) R. A. Grieger, C. A. Eckert, *Ind. Eng. Chem. Fundam.* **10** (1971) 369.

¹⁰) B. E. Poling, C. A. Eckert, *ibid.* **11** (1971) 451.

¹¹) J. R. McCabe, C. A. Eckert, *ibid.* **13** (1974) 168.

¹²) J. R. McCabe, C. A. Eckert, *Acc. Chem. Res.* **7** (1974) 251.

¹³) C. Brun, G. Jenner, *Tetrahedron* **28** (1972) 3113.

¹⁴) J. Rimmelin, G. Jenner, *ibid.* **30** (1974) 3081.

¹⁵) J. Papadopoulos, G. Jenner, *Bull. Soc. Chim. Fr.* **II** (1982) 313. Although the authors favor a concerted mechanism, they say that partial interference of a stepwise mechanism cannot be excluded.

¹⁶) G. Jenner, *ibid.* **II** (1984) 275.

¹⁷) K. Seguchi, A. Sera, K. Maruyama, *Bull. Chem. Soc. Jpn.* **47** (1974) 2242.

¹⁸) G. Swieton, H. Kelm, *J. Chem. Soc., Perkin Trans. 2*, **1979**, 519.

¹⁹) B. S. El'yanov, S. K. Shakhova, B. D. Polkovnikov, L. F. Rar, *ibid.* **1985**, 11.

²⁰) Using a similar argument, by comparing ΔV^* for all products in the dimerization of chloroprene, C. A. Stewart, *J. Am. Chem. Soc.* **94** (1972) 635, found in favor of the concerted mechanism for most of the [2 + 4] cycloadducts (–30 cm³/mol) as opposed to the [2 + 2] products formed stepwise (–22 cm³/mol), although one [2 + 4] dimer fell into the stepwise category (–22 cm³/mol). By an analogous strategy, similar conclusions were reached for the dimerization of 1,3-cyclohexadiene: F.-G. Klärner, B. M. J. Dogan, O. Ermer, W. von E. Doering, M. P. Cohen, *Angew. Chem. Int. Ed. Engl.* **25** (1986) 108; *Angew. Chem.* **98** (1986) 109.

²¹) R. P. Bell, *Proc. Roy. Soc. London, Ser. A*, **154** (1936) 414; M. G. Evans, M. Polanyi, *Trans. Faraday Soc.* **32** (1936) 1340; G. S. Hammond, *J. Am. Chem. Soc.* **77** (1955) 334.

²²) J. Sauer, *Angew. Chem. Int. Ed.* **6** (1967) 16; *Angew. Chem.* **79** (1967) 76.

²³) R. Huisgen, R. Schug, *J. Am. Chem. Soc.* **98** (1976) 7819. The authors say that the DA reaction "has an early TS which resembles the two-plane orientation complex of the reactants" with "little change in bond energy (from the reactants)".

²⁴) The suggestion has been made in ref.²³, p. 440, that the nuclei in a concerted DA approach their final places closely before the electrons will flow to theirs, in order to reconcile the volume criterion, which indicates a late TS, with the energy criterion, which indicates an early TS. We believe, however, that this conflicts with the Born-Oppenheimer approximation.

²⁵) G. Jenner, M. Papadopoulos, J. Rimmelin, *J. Org. Chem.* **48** (1983) 748.

²⁶) Ref.²³, p. 440.

²⁷) Ref.²³, pp. 446.

²⁸) K. Seguchi, A. Sera, K. Maruyama, *Tetrahedron Lett.* **1973**, 1585.

²⁹) S. D. Hamann, in *High Pressure Physics and Chemistry* (R. S. Bradley, Ed.), vol. 2, ch. 7, Academic Press, New York 1963. Hamann's calculation, which predates ours and agrees with it, was brought to our attention after the completion of the project.

³⁰) L. A. Burke, G. Leroy, *Theor. Chim. Acta* **44** (1977) 219.

³¹) A Referee pointed out a case of the same phenomenon in another reaction (solvolysis), in which the bonding change in the TS (stretching) is overwhelmed at atmospheric pressure by solvent-packing effects (contraction from electrostriction). The intrinsic volume change for the reaction was here revealed by using very high pressure, which cancelled the contraction from electrostriction by crushing out the empty space in the ground state; C. Cameron, P. P. S. Saluja, M. A. Floriano, E. Whalley, *J. Phys. Chem.* **92** (1988) 3417.

³²) CRC Handbook of Chemistry and Physics, 54th ed., 1973–1974.

³³) We are not the first to point out the important role played by changes in empty space in determining ΔV for DA reactions, but our conclusions are unique. Refs.^{34–36} came to our attention after the completion of our calculations. Asano and le Noble³⁴ calculated ΔV 's ranging from –9 to –12 cm³/mol. These are 24–36% ΔV 's, a larger fraction than our calculated ΔV 's (11–16%) but still small enough to evoke a cogent discussion of "void" contributions to ΔV and ΔV^* . El'yanov, Shakhova and Rubtsov expressed similar thoughts³⁵). Yoshimura, Osugi and Nakahara³⁶) calculated van der Waals volume changes for one prototype case, also recognizing that packing fraction plays a role in bridging the gap between macroscopic and van der Waals volume (IMV) changes. Thus, they say "The changes in the van der Waals volume for ... 1,3-dipolar cycloaddition ... are ... much smaller than the observed activation and reaction volumes ... The most important factor ... is the size dependence

of the packing coefficient." However, perhaps because no one before us has done accurate and extensive calculations on molecular volumes for DA reactions, and none at all on transition states, refs.³⁴⁻³⁶ are not even mentioned in refs.¹⁻³², nor do they depart from conventional reasoning that assigns the DA reaction to the concerted category. They thereby join all previous authors in reaching conclusions diametrically opposed to ours.

³⁴ T. Asano, W. J. le Noble, *Rev. Phys. Chem. Jpn.* **43** (1973) 82.

³⁵ B. S. El'yanov, S. K. Shakhova, G. A. Rubtsov, *Izv. Akad. Nauk SSSR, Ser. Khim.* **1975**, 2678; *Chem. Abstr.* **84** (1976) 73318d.

³⁶ Y. Yoshimura, J. Osugi, M. Nakahara, *J. Am. Chem. Soc.* **105** (1983) 5414. See also *Bull. Chem. Soc. Jpn.* **56** (1983) 680.

³⁷ J. A. Montgomery Jr., D. Chandler, B. J. Berne, *J. Chem. Phys.* **70** (1979) 4056, conclude from trajectory studies of the *trans-gauche* isomerization of *n*-butane in liquids that transition-state theory overestimates the rate constant by a factor of 2 or 3, that the transmission coefficient is a function of pressure as well as temperature, and that ΔV^\ddagger therefore is negative by several cm^3 /

mole. They suggest that this might explain $|\Delta V^\ddagger| > |\Delta V|$ for some DA reactions. It is not clear, however, that this conclusion can be extrapolated from a very low- E_a reaction (single-bond rotation) to a relatively high- E_a reaction (DA).

³⁸ Another contributor to ΔV^\ddagger might be the increase in solvent viscosity that occurs at high pressure. In an experimental measurement of rate vs. solvent viscosity for a DA reaction, the rate increased with viscosity, and it was pointed out that this imposed an apparent $-\Delta V^\ddagger$ on the kinetics that might be a significant contributor to the calculated ΔV^\ddagger . R. A. Firestone, M. A. Vitale, *J. Org. Chem.* **46** (1981) 2160.

³⁹ R. A. Firestone, *J. Org. Chem.* **33** (1968) 2285; *Tetrahedron* **33** (1977) 3009.

⁴⁰ A program to perform these calculations is available from QCPE: MOLSV.

⁴¹ J. A. Pople, D. L. Beveridge, *Approximate Molecular Orbital Theory*, McGraw-Hill, New York 1970.

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