Reply to “Comment on ‘Phantom Activation Volumes’”

Raymond A. Firestone* and Kevin A. Swiss‡

Department of Medicinal Chemistry, Boehringer Ingelheim Pharmaceuticals, Inc., 900 Ridgebury Road, Ridgefield, Connecticut 06877-0368

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In 2000, we published a paper entitled “Phantom Activation Volumes” (PAV), presenting the idea that some volumes of activation (Va) measured in the usual way include a “phantom” (unreal) component because these reactions are accelerated by raised viscosity, even at atmospheric pressure.[1] That viscosity can accelerate reactions was shown by us in four different cases,[2−4] and there are several more in the literature (vide infra).

Our PAV paper apparently struck a sensitive nerve in the group of le Noble and his close associates, who have attacked it three times in the past three years. Their first Comment claimed that the concept of a nonvolume-based kinetic effect of pressure contradicts the transition state theory.[5] We presented a rebuttal.[6] Next, van Eldik repeated one of our four experiments, claiming that our results were incorrect.[7] That paper was refuted.[8] Now Hamann and le Noble (H&L) say that our kinetic data in a different one of our four experiments do not really show a viscosity−rate correlation.[9] We reply to their principal points.

H&L’s statement in the Introduction that “only two ... approaches ... support the concerted nature of [symmetry-]allowed reactions: stereochemistry and piezochemistry” is wrong with respect to stereochemistry. “The iconoclast may ... maintain that ... the [diradical] intermediate was too short-lived to permit such rotations ....” The iconoclast’s position is a strong one, because there are plenty of data showing single-bond rotation of radical centers slower than cleavage or cyclization.[10−13] The bona fide primary−secondary diradical 3-methylpentane-1,4-diyl, under conditions close to those experienced during typical Diels−Alder (DA) reactions (120° in *n*-octane), closes 3.1−4.9 times faster than it rotates and cleaves 7.5−14.6 times faster than it rotates.[14] These are minimum numbers because N_2 extrusion might be stepwise, and there is a strain barrier to four-ring closure.[15] Using heavy atom effects, we have uncovered DA diradical intermediates whose cleavage/cyclization rates are 1000 times faster than rotation.[16]

Reference 3: “However, Houk and Firestone have reported that the cycloaddition of *cis*- and *trans*-1,2-dideuterioethylene to arylnitrile oxides occurs with at least 98% retention of the configuration; the barrier to rotation of the Ar−CNO−CHD−CHD diradical was estimated to be ‘at most 0.4 kcal/mol’”. With 98% retention the diradical’s barrier to rotation is at most 2.3 kcal/mol, *not* 0.4, as Houk et al. correctly reported.[17] The 0.4 figure came not from their experiment, but from a reference to another paper in which the barrier to rotation of 1-Pr$^\bullet$ was estimated at 0.4 but could have been as high as 3.1 kcal/mol.[19]

Piezochemistry also provides no support for concert. “Because the activation volume (Va) of Diels−Alder reactions thought to be concerted is generally close in magnitude to the overall reaction volume, the argument is that both bonds must have made significant progress toward formation when the transition state is reached.” It is surprising that le Noble says this, because his 1973 article was the first to say that the principal component (72−77% in most cases) of Va is not progress in bonding at all, but rather contraction of empty space.[19] Accurate calculations of molecular and transition state (TS) volumes show that in a DA cycloaddition, only ∼3−5% of Va actually arises from bond formation in the TS, irrespective of whether the mechanism is concerted or stepwise.[20] This is within the uncertainty in Va. Therefore, whatever degree of progress the new bonds have made in the TS is essentially irrelevant to the Va. What really controls Va is the high packing coefficient (PC) of the cyclic TS (if concerted) or the cyclo diradical (if stepwise).[20] In the same vein, Klärner says “the effect on volumes caused by the change in bond lengths is rather small”.[21] For this reason, the high-pressure approach does not tell us anything significant about (1) bond formation in the TS or (2) what the mechanism is. The Stewart−Klärner high-pressure papers cited by H&L indeed make an interesting case for duality of mechanism in chloroprene dimerization,[21,22] but when heavy atom effects are taken into account their data can also be reconciled to a single stepwise mechanism.[13]

“S&F ... argued that the activation volume needs to be corrected because it is partly of a phantom nature, and that when this is done, the remaining and presumably real part is insufficient to support the claim of concertedness”. This incorrectly implies that only by separating PAV’s from real Va’s can we oppose the claim of concert. Actually (vide supra), it is PC,[20] not PAV, that shows that concert is not provable by high-pressure kinetics. What PAV can do is explain the paradox that in some DA’s the TS is apparently smaller than the cycloadduct, an otherwise inexplicable phenomenon.[1]

H&L claim that van Eldik’s experiments, which found no viscosity dependence on cyclopentadiene (CPD) dimerization,[7] are of “unquestionably superior quality” to ours, which did find a viscosity dependence.[4] But van Eldik’s experiments were in fact unquestionably *inferior* to ours, to wit:[8] their CPD was clearly impure, being not miscible with some hydrocarbons, whereas ours was miscible in all; their CPD gave rise to insoluble polymers, whereas ours did not; their rate constants were sometimes crude (see, e.g., their Figures 3 and 4, especially 4, where *k* wanders greatly as the reaction proceeds) but were reported as precise; they did not measure viscosities of their reaction mixtures as we did, and their viscosities uncorrected for 10% 1-chlorobutane *had* to be wrong. No previous author has ever reported cloudiness or precipitates during this reaction in many varied solvents. Most important, their stirring was insufficient to dissipate the heat evolved, which surely affected their rate constants significantly; this factor alone invalidates the entire study.

In the past, moreover, CPD dimerization has shown then-unrecognized viscosity effects similar to ours (Table 1). A 1939 study reported that rates in a few common solvents at 35° vary little and are unrelated to polarity. However, the rate in paraffin oil exceeds all the others, e.g., twice that in CCl_4 and 2.8 times that in monomeric CPD itself. The rate in $(CPD)_2$ exceeds those in CCl_4 and CPD by 2.4 and 3.3 times, respectively.[23] Those

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* Corresponding author. E-mail: rfiresto@rdg.boehringer-ingelheim.com. Phone: 203-798-4141. Fax: 203-791-6072.

‡ Present address: Inex Pharm. Corp., 100-8900 Glenlyon Pkwy, Burnaby BC V5J5J8, Canada.

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TABLE 1: Rate vs Viscosity in CPD Dimerization[23]

solvent	rel rate, 35°	rel Rate, 35°	rel rate, 136°
CPD	0.36	0.30	
CCl_4	0.5	0.42	
paraffin oil	1		1
$(CPD)_2$		1	
gas phase			0.22

TABLE 2: Rate vs Viscosity in a 1,3-Dipolar Cycloaddition[26]

solvent	viscosity, cP, 30°	rel rate
mesitylene	0.23	92
p-cymene	0.32	99
decalin	0.45−0.58	220
paraffin oil	2−3	237

accelerations, which we attribute to viscosity, are close to those we observed (2.5 times) in dodecane vs *n*-octane.[1] The rate in paraffin oil is 4.5 times that in the gas phase at 136°, i.e., across a significant discontinuity in viscosity, a phenomenon commonly observed.[2]

A 1968 study reported rates for CPD dimerization in 16 common solvents, probing to no avail for a correlation with any of 8 solvent properties—just about every property then considered significant—e.g., dielectric constant, Hildebrand's solvation parameter δ, etc.[24] However, we found that in those data there is a good correlation between rate and viscosity (Figure 1 in ref 4), with slope in the same range (0.60−1.28/cP) as ours (1.87/cP).

Thus, van Eldik's study is flawed and cannot be used to disprove ours. It should also be noted that we have observed, under very different conditions, viscosity-induced acceleration of three other thermal pericyclic reactions, both unimolecular, viz. an intramolecular DA[2,4] and a Claisen rearrangement,[2,3] and bimolecular, a 1,3-dipolar cycloaddition (1,3-DC).[4] The slopes were smaller than for CPD dimerization, but the acceleration for the Claisen rearrangement, extrapolated to polyethylene as solvent by using a mixed solvent to avoid the onset of encounter control, reached at least 12.8 times.[3]

"S&F further used their data to support the concept of 'vibrational activation', in which the cycloaddition process requires 'reactants', one of which is vibrationally excited'". There, H&L quote us correctly. We proposed this in 1973, and from it derived the prediction that some bond-forming reaction rates would rise with viscosity.[25] However, the fact that they do, though it supports the theory, does not prove it, as we pointed out in our first viscosity paper.[2] Viscosity-induced acceleration stands on its own facts regardless of the validity of the vibrational-activation theory.

In the 1,3-DC of ethyl phenylpropiolate (EPP) and diphenyl diazomethane (DDM), where we reported a rise and then fall in rate with rising viscosity, H&L report that our data, which are the quotients of the slope of ln [DDM]/time and the ratio [EPP]/[DDM], when recalculated by a standard kinetic equation, give a different result. They find that the rise in rate with viscosity is not really there, and in this particular example we cannot refute their argument.

However, it is not justified to extrapolate from this one reaction to all the others, or even to all 1,3-DC's. There is in fact an outstanding case in the literature of a 1,3-DC whose rates rise sharply with viscosity just as we reported, only more so.[26,27] EPP, the same dipolarophile we used, reacts with C-methyl-N-phenyl sydnone at 140° in, inter alia, four solvents with dielectric constants almost identical (Table 2). The acceleration from lowest to highest viscosity is 2.58 times. This is more dramatic than our own reported acceleration with the same dipolarophile at 30° (1.16 times) but the curve is of the same form, and makes the same point independently of our own experiments.

In addition, there are many other precedents mentioned above—CPD dimerization,[4,23,24] intramolecular DA,[2,4] and Claisen.[2,3] Therefore pronounced viscosity effects on 1,3-DC as well as several other thermal pericyclic reactions, and thus the PAV concept, stand on firm ground.[28]

In the gas phase, the rate of dimerization of benzyl radicals in Ar at 300 K increases with pressure above 1 atm to the onset of diffusion control at about 100 atm.[31] Viscosity could be the active principle. A PAV ascribed to the effect of pressure on solvent dielectric constant instead of viscosity has been reported.[32]

The roster of DA reactions that respond to viscosity exactly as ours do has been greatly expanded in a recent paper comparing rate vs viscosity for nine different examples in a very wide variety of solvents.[33] In every case, the rate first rose and then fell as the viscosity was raised, irrespective of the nature (polar or nonpolar) of the solvent. The rates peaked at 0.8−1.2 cP, for the most part near 1.2, where ours did for CPD dimerization.[4] The primacy of viscosity over other solvent properties in this study is just what we saw in two earlier studies of CPD dimerization[23,24] (vide supra). This overwhelming body of data should be sufficient to bring this controversy to an end.

References and Notes

(1) Swiss, K. A.; Firestone, R. A. *J. Phys. Chem.* **2000**, *104*, 3057.
(2) Firestone, R. A.; Vitale, M. A. *J. Org. Chem.* **1981**, *46*, 2160.
(3) Swiss, K. A.; Firestone, R. A. *J. Org. Chem.* **1999**, *64*, 2158.
(4) Swiss, K. A.; Firestone, R. A. *J. Phys. Chem. A* **1999**, *103*, 5369.
(5) le Noble, W. J.; Asano, T. *J. Phys. Chem. A* **2001**, *105*, 3428.
(6) Firestone, R. A.; Swiss, K. A. *J. Phys. Chem. A* **2001**, *105*, 3430.
(7) Weber, C. F.; van Eldik, R. *J. Phys. Chem. A* **2002**, *106*, 6904.
(8) Firestone, R. A.; Swiss, K. A. *J. Phys. Chem. A* **2002**, *106*, 6909.
(9) Hamann, S. D.; le Noble, W. J. *J. Phys. Chem. A* **2003**, *107*, 7121.
(10) Firestone, R. A. *J. Org. Chem.* **1968**, *33*, 2285.
(11) Firestone, R. A. *Tetrahedron* **1977**, *33*, 3009.
(12) Firestone, R. A. *Heterocycles* **1987**, *25*, 61.
(13) Firestone, R. A. *Tetrahedron* **1996**, *52*, 14459.
(14) Dervan, P. B.; Uyehara, T. *J. Am. Chem. Soc.* **1979**, *101*, 2076.
(15) Pedersen, S.; Herek, J. L.; Zewail, A. H. *Science* **1994**, *266*, 1359.
(16) Telan, L. A.; Firestone, R. A. *Tetrahedron* **1999**, *55*, 14269.
(17) Houk, K. N.; Firestone, R. A.; Munchausen, L. L.; Mueller, P. H.; Arison, B. A.; Garcia, L. A. *J. Am. Chem. Soc.* **1985**, *107*, 7227.
(18) Krusic, P. J.; Meakin, P.; Jesson, J. P. *J. Phys. Chem.* **1971**, *75*, 3438.
(19) Asano, T.; le Noble, W. J. *Rev. Phys. Chem. Jpn.* **1973**, *43*, 82, Table 7.
(20) Firestone, R. A.; Smith, G. M. *Chem. Ber* **1989**, *122*, 1089.
(21) Klärner, F.-G.; Krawczyk, B.; Ruster, V.; Deiters, U. K. *J. Am. Chem. Soc.* **1994**, *116*, 7646.
(22) Stewart, C. A., Jr. *J. Am. Chem. Soc.* **1971**, *93*, 4815.
(23) Benford, G. A.; Kaufmann, H.; Khambata, B. S.; Wasserman, A. *J. Chem. Soc.* **1939**, 381. Khambata, B. S.; Wasserman, A. *J. Chem. Soc.* **1939**, 371. Benford, G. A.; Wasserman, A. *J. Chem. Soc.* **1939**, 362.
(24) Cöster, G.; Pfeil, E. *Chem. Ber.* **1968**, *101*, 1, 4248.
(25) Firestone, R. A.; Christensen, B. G. *Tetrahedron Lett.* **1973**, 389.
(26) Huisgen, R.; Gotthardt, H. *Chem. Ber.* **1968**, *101*, 1059.
(27) There may be an even higher peak in rate at a viscosity between those of Decalin and paraffin oil.
(28) It is curious that Hamann joins in criticizing the PAV concept, because he supplied an early example of a PAV himself: Hamann, S. D. *Trans. Faraday Soc.* **1958**, 507. The rates of etherification of ethyl bromide with alkoxides rise with pressure, but some then fall as the pressure rises further, which he attributes to the onset of diffusion control at high viscosity. Thus the apparent Va changes from negative to positive in this region, whereas the intrinsic Va undoubtedly does not. Here, then, is a clear-cut example of a PAV. The termination of free-radical polymerization behaves in the same way: Nicholson, A. E.; Norrish, R. G. W. *Discuss. Faraday Soc.* **1956**, *22*, 97. Of course, diffusion control always creates a positive contribution to Va,[5] but the fact that we understand the origin of a PAV does not diminish its importance.[6] Furthermore, Hamann's data suggest viscosity-induced acceleration of this reaction, i.e., a *second* PAV hidden

in this paper. Going from 1 to 10 000 atm (well below diffusion control), alkylation of isopropoxide in IPA accelerates 1.59 times more than methoxide in MeOH despite a viscosity increase 16 times greater for IPA than MeOH. Because the intrinsic Va's of both reactions are probably similar,[29] and because the less polar IPA probably exceeds MeOH in electrostriction[30] in forming the alkoxide's solvent shell, which must be shed (a volume-increasing event) before reaction can proceed, one would naively expect isopropoxide to accelerate *less*, not more, than methoxide with rising pressure. Viscosity-induced acceleration (which gives rise to another PAV) resolves this discrepancy. For yet other examples of PAV's from members of this circle (Asano, van Eldik) see: (a) ref 1, p 3057; (b) Dolidze, T. D.; Khoshtariya, D. E.; Waldeck, D. H.; Macyk, J.; van Eldik, R. *J. Phys. Chem. B* **2003**, *107*, 7172, in which the "positive volume of activation [for a Cytochrome C electrode process] results from the pressure-induced increase of the protein's intrinsic viscosity", because a true volume effect would be expected to be negative. Thus our[1] and van Eldik's PAV's arise in exactly the same way, from pressure-induced viscosity increases.

(29) Asano, T.; le Noble, W. J. *Chem. Rev.* **1978**, *78*, 407. See Table 2, pp 520−524.

(30) Reichardt, C. *Solvent Effects in Organic Chemistry*; Verlag Chemie: Weinheim, Germany, 1979; p 184.

(31) Oum, K.; Sekiguchi, K.; Luther, K.; Troe, J. *Phys. Chem. Chem. Phys.* **2003**, *5*, 2931.

(32) Kiselev, V. D.; Kashaeva, E. A.; Konovalov, A. I. *Tetrahedron* **1999**, *55*, 1153. The penultimate columns in Tables 5 and 6 are PAV's.

(33) Kumar, A.; Deshpande, S. S. *J. Org. Chem.* **2003**, *68*, 5411.