Scheme I

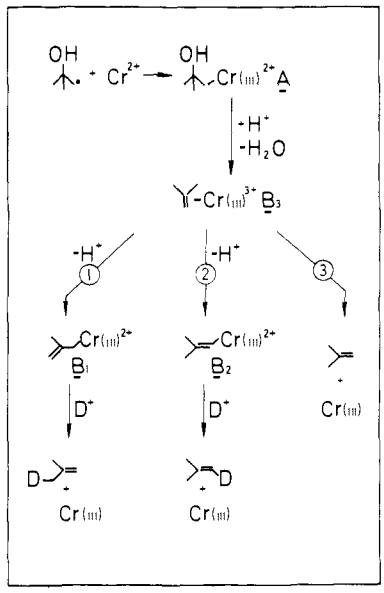


Table I. Partial Mass Spectra of 2-Methylpropene[a]

	intensity		
m/e	unlabeled[c]	experiment I	experiment II
41	1000[b]	1000[b]	1000[b]
42	38	45	57
55	186	187	165
56	461	469	414
57	22	26	24

[a] An Atlas Mass Spectrometer Model CH4 with 70-eV electrons in the ionization chamber was used. [b] Arbitrary units. [c] Same conditions as experiment I using H_2O in place of D_2O.

the parent fragment ion. On the other hand, $CHD{=}C(CH_3)_2$, formed via path 2, would produce a mass spectrum with full deuterium incorporation in both the molecular ion and the parent fragment ion.

Generation of the free radical precursors to A and B were carried out under two different experimental conditions. Helium-saturated D_2O containing *t*-BuOH (0.5 M), H_2O_2 (0.005 M), and Cr(II) (0.05 M) was made acidic with either $HClO_4$ (0.010 M, experiment I) or AcOH/AcONa (pH 4.7, total acetate = 0.012 M, experiment II). The deuterium content of the two solutions was established to be not less than 95% for both experiments.[7] The partial mass spectra produced by gas samples obtained from the two sets of experimental conditions are given in the table.

The 2-methylpropene produced in experiments I and II is almost identical with unlabeled 2-methylpropene indicating that little or no incorporation of deuterium occurs in these systems. Control experiments failed to detect any 2-methylpropene when Cr(II) was omitted from the reaction mixture, which confirms the A → B → 2-methylpropene sequence as the source of the unlabeled 2-methylpropene. The failure to observe deuterated 2-methylpropene rules out any significant participation of paths 1 and 2 in the formation of the alkene product. These results can be readily explained by identifying the alkenechromium complex, B-3, as the long-lived species B, which then undergoes subsequent decomposition releasing Cr(III) and 2-methylpropene directly (Scheme I, path 3). Even when a large primary kinetic isotope effect (k_H/k_D = 10) is assumed for the cleavage of the alkylchromium complexes, B-1 and B-2, less than 5% of the 2-methylpropene formation can be assigned to paths 1 and 2.

The simplest mechanism (Scheme I, path 3) consistent with these results requires that under the proper conditions $[(H_2O)_5Cr(CH_2{=}C(CH_3)_2)]^{3+}$, B-3, is an observable, surprisingly long-lived, species whose UV–vis spectrum is deceptively similar to those of alkyl chromium complexes.[9] Implicit in this mechanism is the assumption that electrophilic attack on alkylmetal complexes need not always be prefertially directed toward the metal–carbon bond. Loss of the hydroxyl group in A to generate an alkene complex, B-3, is formally the reverse reaction of nucleophilic attack on a metal-coordinated olefin by H_2O such as might occur in the Wacker process.[10] We intend to investigate the mechanism of the decomposition of other β-hydroxyalkyl complexes of chromium and of other metals as well.

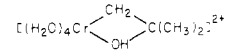
Acknowledgment. We thank Prof. A. Streitweiser and Prof. J. H. Espenson for helpful discussions and D. Carmi for technical assistance. This work was supported in part by a grant from the United States–Israel Binational Science Foundation (B.S.F.) Jerusalem, Israel.

Registry No. A, 51965-50-5; B-3, 88801-82-5; 2-methylpropene, 115-11-7.

(7) Deuterium content of the aqueous reaction mixtures was determined from a mass spectrum of the hydrogen gas evolved by the thermal reaction of dry zinc powder with a few drops of the aqueous mixture. Incomplete drying of the zinc powder could produce a low analysis for deuterium.

(8) Gas samples were passed through a cold trap prior to analysis in order to remove *t*-BuOH vapors. Residual *t*-BuOH produces fragment ions of *m/e* 59, 57, 56, 52, and 41. The data in Table I have been corrected for the small contributions of fragment ions derived from *t*-BuOH by use of a mass spectrum of pure *t*-BuOH.

(9) One of the reviewers has suggested that the observed intermediate is



and not B_3. This intermediate might be formed by the labilizing effect of the alkyl–chrome bond on the Cr–OH_2 bond. However, the rate of formation of the intermediate[4] is over 2 orders of magnitude faster than the expected labilization of the trans Cr–OH_2 bond[1] and that of the cis bonds is even lower.[1] Furthermore it is difficult to envisage why the transformation of A into this intermediate would be acid catalyzed in the strongly acidic pH range.[1,4] In order to check this possibility we measured the rate of the A to B transformation for *trans*-$CrL(H_2O)CH_2C(CH_3)_2OH^{2+}$, where L = 1,4,8,12-tetraazacyclopentadecane, in neutral solutions. The specific rate of reaction observed under these conditions is $(1.0 \pm 0.2) \times 10^2\ s^{-1}$, i.e, identical with that observed for the aquo complex. This result clearly rules out any major role of the cis Cr–OH_2 bond.

(10) Backvall, J. E.; Akermerk, B.; Lyunggrer, S. O. *J. Am. Chem. Soc.* **1979**, *101*, 2411. No proposal is made here regarding the stereochemistry of the dehydration step or the fate of the lost hydroxyl group.

Allenic Amino Acids. 1. Synthesis of γ-Allenic GABA by a Novel Aza-Cope Rearrangement[1]

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The concept of enzyme suicide inhibition has been a powerful and intellectually appealing strategy for the design of specific enzyme inactivators.[2-6] Some of the most effective inactivators are acetylenic substrates that have been designed to exploit the high reactivity to Michael addition that is characteristic of a triple bond (or allene) when it is brought into conjugation with strongly electron-withdrawing groups. Thus, considerable success has been achieved toward inhibiting vitamin B_6 linked decarboxylases and transaminases by using the target enzyme to unmask the latent

(1) Contribution No. 183 from the Institute of Bio-Organic Chemistry, Syntex Research.

(2) Rando, R. R. *Science (Washington, D.C.)* **1974**, *185*, 320; *Acc. Chem. Res.* **1975**, *8*, 281.

(3) Abeles, R. H.; Maycock, A. L. *Acc. Chem. Res.* **1976**, *9*, 313.

(4) Walsh, C. In "Horizons in Biochemistry and Biophysics"; Quagliariello, E., Palmieri, F., Singer, T. P., Eds.; Addison-Wesley: Reading, MA, 1977; Vol. 3, p 36; *Tetrahedron* **1982**, *38*, 871; *Trends Pharmacol. Sci.* **1983**, 254.

(5) (a) Metcalfe, B. W. *Annu. Rep. Med. Chem.* **1981**, *16*, 289. (b) Bey, P.; Metcalfe, B.; Jung, M. J.; Fozard, J.; Koch-Weser, J. In "Strategy in Drug Research"; Keverling Brusman, J. A., Ed.; Elsevier: Amsterdam, 1982; p 89.

(6) Rando, R. R. *Methods Enzymol.* **1977**, *46*, 158.

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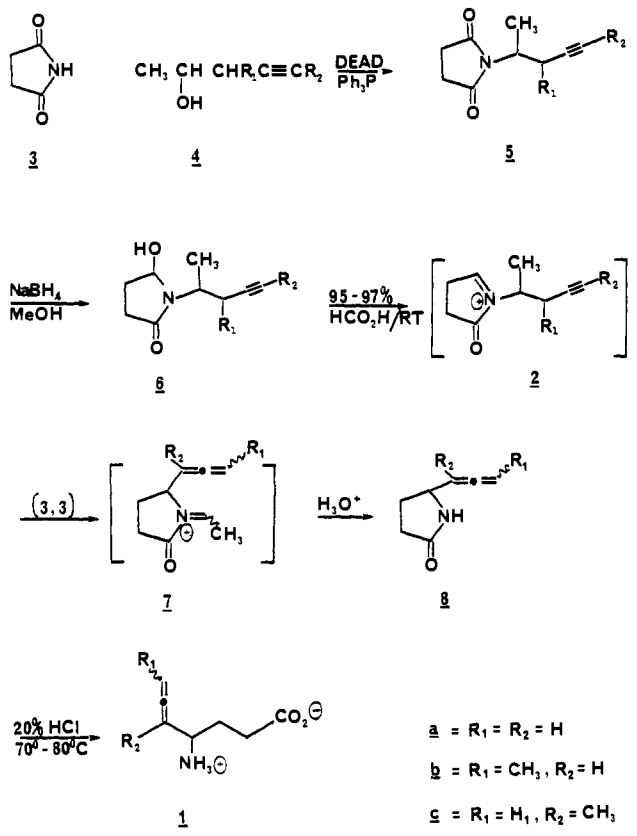
Scheme I



reactivity of relevant β,γ-acetylenic amines and amino acids.[7,8]

Despite the mechanistic rationale for "suicide inhibition", the corresponding allenic amino acids have not been described.[7,9] This is unfortunate as allenes are of special interest because they can be made chiral and thus offer possibilities for specific enzyme inhibition that are not available to acetylenes.[10]

We now wish to report the first example of the synthesis of a parent allenic amino acid, 4-amino-5,6-heptadienoic acid (γ-allenic GABA, **1a**), which is both a potent and specific inhibitor of mammalian GABA transaminase[11] (4-aminobutyrate:2-oxoglutarate aminotransferase [EC 2.6.1.19]).

The preparation of **1a** features a novel aza-Cope rearrangement[12-14] of the acyliminium ion **2a** and is accomplished in essentially four steps as described in Scheme I. Condensation of succinimide (**3**) with 4-pentyn-2-ol (**4a**) in THF in the presence of Ph_3P and diethyl azodicarboxylate[15] gave 2-(*N*-succinimidyl)-4-pentyne (**5a**) (45%), which was in turn reduced with sodium borohydride in methanol (0 °C) to a mixture of hydroxy lactams **6a**[16] (65%). The hydroxy lactams (**6a**) in 95–97% HCO_2H[12,13] were allowed to stand for 3–5 days at room temperature, after which the mixture was concentrated, and the γ-allenic pyrrolidone[17,18] **8a** was isolated (35%) by flash chromatography on SiO_2. When the lactam **8a** was hydrolyzed overnight in 20% HCl (80 °C) the hydrochloride salt of **1a** was obtained. Ion exchange chromatography of the latter (20% pyridine–H_2O) followed by crystallization from acetone–water gave γ-allenic GABA (**1a**).[19] In this fashion the alkyl derivatives of allenic GABA, **1b** and **1c**, can be prepared from the corresponding hydroxy lactams,[20] **6b** and **6c**. It is to be noted that the rearrangement of *threo*-**6b** gives a 9:1 ratio of diastereomeric 4-amino-5,6-octadienoic acids **1b**. We are currently exploring the specificity of this rearrangement.

Hart[12,21] and Speckamp[13,22-24] have elegantly demonstrated the utility of α-acyliminum ions in the construction of fused heterocyclic systems, by exploiting π-cyclization reactions of olefinic-,[12,13,24] allenic,[23] and acetylenic[22] functions. In some cases aza-Cope rearrangements underlie the π-cyclization reactions.[12,13,21,24] A factor critical to the success of the rearrangement of **2** that leads to significant amounts of isolated **8** is the pattern of substitution on the exo-carbon attached to nitrogen of the hydroxy lactams. Apparently, CH_2[22] in place of $CHCH_3$ in **6** does not lead to allenic pyrrolidones upon workup.[25,26] Our work, in fact, represents the first example of an aza-Cope rearrangement in which a propargyl function has been converted to an allene.

The availability of **1** will allow an interesting comparison among olefinic, acetylenic, and allenic functionalities in their abilities to inactivate GABA transaminases. Mammalian GABA-T has been a frequent target of suicide inhibitors because it is a primary catabolic enzyme for GABA, a major inhibitory neurotransmitter in the CNS. Both vinyl- and ethynyl-GABA have been reported to be potent inhibitors of mammalian GABA transaminase, and

(7) According to current mechanistic paradigms the mode of action of acetylenic amino acid inactivators involves combination with the enzyme-bound pyridoxal cofactor in the normal fashion followed by enzymic conversion of the adduct to an isomeric acetylenic (or allenic) iminium ion, which then captures a suitably disposed active-site base.[2-6] For a serious alternative mechanistic viewpoint, see: Likos, J. J.; Ueno, H.; Fieldhaus, R. W.; Metzler, D. E. *Biochemistry* **1982**, *21*, 4377.

(8) See: "Enzyme-Activated Irreversible Inhibitors"; Seiler, N., Jung, M. J., Koch-Weser, J., Eds.; Elsevier: Amsterdam, 1978; and references therein.

(9) Only a few allenic suicide substrates have been described. Metcalfe, B. W.; Wright, C. L.; Burkhart, J. B.; Johnson, J. O. *J. Am. Chem. Soc.* **1981**, *103*, 3221: and Ortiz de Montellano, P. R.; Kinze, K. L. *Biochem. Biophys. Res. Commun.* **1980**, 443.

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(11) Pliura, D., unpublished results.

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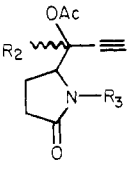
(13) Ent, H.; de Koning, H.; Speckamp, W. N. *Tetrahedron Lett.* **1983**, 2109

(14) Overman, L. E.; Mendelson, L. T. *J. Am. Chem. Soc.* **1981**, *103*, 5579, and references therein.

(15) Mitsunobu, O.; Wada, M.; Sano, T. *J. Am. Chem. Soc.* **1972**, *94*, 679.

(16) Chamberlin, A. R.; Chung, J. Y. L. *Tetrahedron Lett.* **1982**, 2619.

(17) We have also prepared 5-allenylpyrrolidones by reductive displacement on i; i is derived from 5-formyl- or 5-acylpyrrolidones. These results will be presented in the full paper.



i

(18) **8a**: IR ν_{max} 3100–3600, 1955, 1670–1690 cm^{-1}; ^1H NMR δ ($CDCl_3$) 2.0–2.5 (m, 4 H, CH_2), 4.1–4.35 (m, 1 H, CHN), 4.8–4.95 (m, 2 H, CH_2=C=C), 5.05–5.25 (m, 1 H, HC=C=C), 4.9 (broad 1 H, NH).

(19) **1a**: mp 171 °C; IR ν_{max} 1957 cm^{-1} (C=C=C); ^1H NMR δ (D_2O) 1.9–2.5 (m, 4 H, CH_2), 3.7–4.0 (m, 1 H, CHN), 5.1 (app dd, 2 H, H_2C=C=C), 5.3 (app t, 1 H, HC=C=C); ^{13}C NMR δ (D_2O) 32.0 (t, CH_2), 36.1 (t, CH_2), 52.5 (d, CHN), 82.(t, H_2C=C=C), 90.5 (d, HC=C=C), 183.0 (s, CO_2), 210 (s, C=C=C). Anal. Calcd for $C_{17}H_{11}NO_2H_2O$: C, 52.82; H, 8.23, N, 8.80. Found: C, 52.67; H, 8.07; N, 8.79.

(20) (a) **1b**: IR ν_{max} = 1965 cm^{-1}; ^1H NMR δ(D_2O) 1.7 (dd, 3 H, J = 3.3, 7.1 Hz, CH_3), 1.7–2.4 (m, 4 H, CH_2), 3.6–3.9 (m, 1 H, CHN), 5.1–5.7 (m, 2H, CH=C=CH); ^{13}C NMR (δ D_2O): 16.00 (CH_3), 32.06 (CH_2CHN), 36.11 (CH_2CO_2H), 52.74, 52.97 (CHN), 90.69 (CH_2CH), 93.93, 94.08 (*C*HCHN), 184.04 (CO_2H), 206.78 (C=*C*=C). **1c**: IR ν_{max} 1957 cm^{-1}; ^1H NMR (δ (D_2O) 1.6 (app t, 3 H, CH_3), 1.7–2.3 (m, 4 H, CH_2), 3.5–3.75 (m, 1 H, CHN), 4.75–4.95 (m, 2 H, CH_2=C). **1a** and **1c** are racemates. **1b** is a mixture of diastereomers. (b) *Threo*-**6b** is prepared by coupling succinimide with *erythro*-3-methyl-4-pentyn-2-ol (**9**), which in turn is made from *trans*-2,3-epoxybutane (**10**) and lithium acetylide (**11**).

(21) Hart, D. J.; Yang, T. K. *Tetrahedron Lett.* **1982**, 2761; *J. Chem. Soc., Chem. Commun.* **1983**, 135.

(22) Schoemaker, H. E.; Boer-Terpstra, T.; Dijkink, J.; Speckamp, W. N. *Tetrahedron* **1980**, 143.

(23) Nossin, P. M. M.; Speckamp, W. N. *Tetrahedron Lett.* **1981**, 3289.

(24) Nossin, P. M. M.; Hamersma, J. A. M.; Speckamp, W. N. *Tetrahedron Lett.* **1982**, 3807.

(25) The yield of the rearrangement appears to be sensitive to the amount of water in formic acid. Recently, using 20% trifluoroacetic acid in CH_2Cl_2, we have been able to effect the rearrangement of **6a** and *N*-(but-1-yn-4-phenyl-4-yl)-5-hydroxy-2-pyrrolidone in good yield (>80%). Castelhano, A. L., unpublished results to appear in full paper.

(26) That alkyl substitution of the iminium ion carbon in product, i.e., **7**, promotes the Cope rearrangement at the expense of π-cyclization is implicit in the report by Hart (Hart, D. J. *J. Org. Chem.* **1981**, *46*, 367) dealing with *N*-(hept-1-en-4-yl)-2(*E*)-(carbethoxymethylidene)-5-hydroxypyrrolidone.

vinyl-GABA has been in clinical trials.[27-29] Preliminary results indicate that the in vitro activity of allenic GABA compares favorably with its unsaturated analogues. The full results of the synthesis and of enzymological studies of **1a** and related chiral allenes will be reported at a later date.

Acknowledgment. We are indebted to Valerie Robinson for her expert assistance with NMR spectroscopy and to Dr. John Moffatt for a helpful critique of the manuscript.

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(28) Palfreyman, M. G.; Schechter, P. J.; Buckett, W. R.; Tell, G. P.; Koch-Weser, J. *Biochem. Pharmacol.* **1981**, *30*, 817.
(29) Allen, R. D.; Johnston, G. A. R. *Med. Res. Rev.* **1983**, 91.

Identification of Classical S_N2 and Ion–Molecule Pair Mechanisms in the Second-Order Piperidine Displacement of Pyridines from *N*-Benzylpyridinium Cations

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In contrast to the plethora of mechanistic investigations of nucleophilic substitution at saturated carbon in neutral substrates with negatively charged leaving groups,[1] relatively little has been published on such reactions involving positively charged substrates and neutral leaving groups.[2] One cardinal difference between these two classes of reactions is that in the former, the unimolecular (S_N1) pathway by definition involves charge separation, and hence it is rarely if ever encountered in solvents of low dielectric constant; by contrast, if the substrate is a cation to begin with, this mechanism may persist even in relatively nonpolar solvents. Thus, extensive investigations have shown that N-substituents in 1,2,6-trisubstitutedpyridinium cations can be transferred to nucleophiles in reactions of preparative value;[3] both first- and second-order kinetics have been shown to occur in such reactions in media such as chlorobenzene, sometimes simultaneously.[4]

We now report kinetic measurements at varying hydrostatic pressures that provide a fascinating insight into the details of the S_N2 mechanism of these reactions. Activation volumes for the traditional *anionic* displacements invariably have moderately negative values ranging from −5 to −15 cm^3/mol.[5] The obvious interpretation of these results has been that the binding of the anionic nucleophile to the neutral substrate proceeds well ahead of the dissociation of the leaving group and that the transition state is more tightly assembled than the separate initial entities. We had no reason to suspect anything fundamentally different from the reaction of a cationic substrate with a neutral nucleophile; in fact, one confirming example has already been reported.[6]

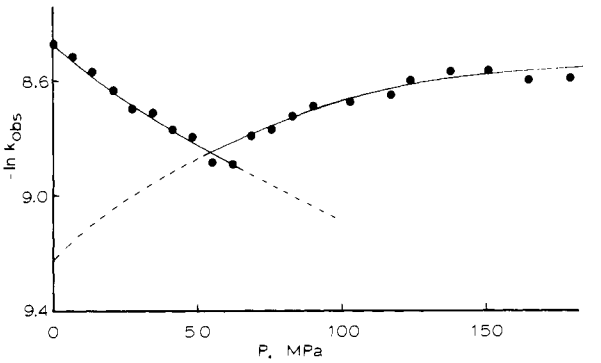
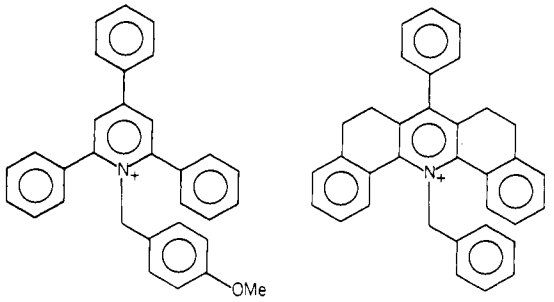


Figure 1. Pseudo-first-order rate constant for the reaction of **2** with piperidine at 30 °C in chlorobenzene as a function of pressure.

At atmospheric pressure and 100 °C, 1-(*p*-methoxybenzyl)-2,4,6-triphenylpyridinium perchlorate (**1**) reacts with piperidine in chlorobenzene predominantly by the first-order route; however, at lower temperatures, a second-order path offers increasing competition ($\Delta H^{\ddagger}$ = 13.6 ± 3.1 kcal/mol, vs. 26.6 ± 3.6 kcal/mol for the first-order path), and at 30 °C it is the only one detectable.[7] When the rate constant at 30 °C was measured in chlorobenzene at elevated pressures by means of UV spectra,[8] we found that $\Delta V^{\ddagger}$ is *positive* at +18.9 ± 1 cm^3/mol; the reaction remains cleanly second order as the pressure is raised. This reaction is clearly dominated by bond *cleavage*, and we postulate that the substrate undergoes heterolysis to give a pyridine–benzyl cation pair (probably in the form of a charge-transfer complex) followed by rate-controlling capture with piperidine.

In order to see whether the more traditional, concerted displacement could be induced to occur, we then examined 1-benzyl-5,6,8,9-tetrahydro-7-phenyldibenz[*a*,*h*]acridinium tetrafluoroborate (**2**) under the same conditions. The absence of the *p*-methoxy group implies diminished stability for the benzyl cation; indeed, first-order behavior has not been detected with this substrate even at elevated temperatures.[7] However, this substrate



1 2

produced an even more surprising result: the usual logarithmic rate vs. pressure plot reveals a plainly visible minimum (see Figure 1, and further comments below). This minimum is of course indicative of competing pathways, with opposite pressure dependence. The low-pressure reaction has a $\Delta V^{\ddagger}$ of ca. +22 cm^3/mol; the high-pressure branch upon extrapolation back to zero pressure is found (with less precision) to have a $\Delta V^{\ddagger}$ of about −20 cm^3/mol.

We see no way to avoid concluding that the result indicates the simultaneous occurrence of the classical S_N2 mechanism and

(1) For review, see: Bentley, T. W.; Schleyer, P. v. R. *Adv. Phys. Org. Chem.* **1977**, *14*, 1.
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(8) The rates were followed by means of a well-thermostated Aminco high-pressure window vessel and a self-adjusting all-quartz optical cell (le Noble, W. J.; Schlott, R. *Rev. Sci. Instrum.* **1976**, *47*, 770). The two solid intersecting curves in the figure represent the logarithm of the sum of the rate constants; they may *not* simply be equated to the individual ln *k* values. These lie well below it. However, at zero pressure the *slopes* are reasonably close to those of the individual mechanisms; if anything, their absolute values are *underestimated*.

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