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.

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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]

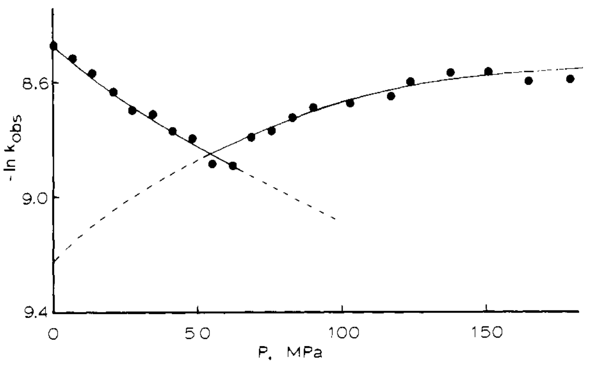
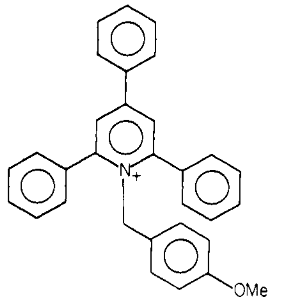


Figure 1. Pseudo-first-order rate constant for the reaction of **2** with piperidine at 30 °C in chlorobenzene as a function of pressure.

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 ($\Delta H^{\ddagger} = 13.6 \pm 3.1$ 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 $+18.9 \pm 1$ 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 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.



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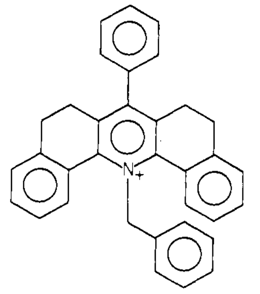

2

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

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of the rate determining nucleophilic attack on an ion–molecule pair, formed in a preequilibrium step. Whereas the latter mechanism is the only one operating in the reaction of the *p*-methoxybenzyl derivative **1** at all pressures investigated, the benzyl derivative **2** reacts predominantly by this path when the pressure is low but by the concerted mechanism when it is high. From the difference $\Delta(\ln k^0)$, the ratio of rate constants at zero pressure is estimated to be 2–2.5; in other words, the ion–molecule pair mechanism contributes 65–70% of the reaction under ambient conditions, and the simple S_N2 reaction accounts for the rest. We point out that the difference in activation volume between these two competing paths, $\Delta\Delta V^{\neq}$ is simply the difference in partial volume between the two isomeric transition states. Its huge value of ca. 40 cm^3/mol is comparable to the reaction volume of the Diels–Alder process—which also relates a pair of states differing by two chemical bonds!

Involvement of the perchlorate and tetrafluoroborate counterions cannot be invoked to explain the minimum. While such involvement has at times bedeviled kinetic high-pressure investigations of electrolytes in media of low polarity,[9] the low (UV) concentrations used here and the demonstrated independence of the rates on the nature of these ions[10] rule out any such complication here.

Although $\Delta V^{\neq}$ had not previously been used as evidence for cation–molecule pairs, one of us has published such evidence implicating anion–molecule pair intermediates.[11] This evidence was subsequently confirmed by means of demonstrations of internal return[12] and of retained configuration.[13] The only precedent for the pair proposed here is the pyridine–trityl cation pair suggested by Streitwieser[14] to explain a special feature of that reaction published by Hughes and Ingold.[15] A closely related development is the intervention of the phenyl cation–nitrogen molecule pair in the dediazonation of benzenediazonium cations reported by Zollinger.[16] Our proposal is reminiscent of that of Sneen,[17] who emphasized that bimolecular nucleophilic displacements of secondary alkyl tosylates and similar *neutral* substrates could occur at the intimate *ion* pair stage of the Winstein solvolysis scheme.[18] That suggestion gave rise to much controversy, and there is no agreement that a genuine case has been recognized; indeed, the *modest*, negative $\Delta V^{\neq}$ values observed in *these* reactions are in better accord with the classical S_N2 model than with prior *ionization*, which is known to be much more powerfully enhanced by pressure ($\Delta V^{\neq}$ *large* and negative).

The shape of the ln *k* vs. *p* curve in the reaction of **2** is a unique example of the traditionally difficult problem of deciphering a reaction subject to competing mechanisms obeying the same observed rate law;[19] one can then obviously not make either pathway dominant by manipulating concentrations. One of us pointed out some 15 years ago[20] that, in those instances in which, first, the two pathways have rates that are not too dissimilar and, second, the faster one possesses a positive activation volume and the slower one is characterized by a negative value, the effect of pressure on the observed rate constant will reveal this kind of duplicity by exposing a minimum. No genuine examples of such plots had been reported to date.[21]

In summary, we have found a unique response of a rate constant to pressure variation. Our results demonstrate that both the classical S_N2 and the ion–molecule pair mechanisms can occur in the title reactions. They compete in one instance, and the extraordinarily large difference in volume (ca. 40 cm^3/mol) between the two transition states leaves no doubt about the nature of their structural difference.

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Solid-State Structure of $[Au_2Li_2(C_6H_4CH_2NMe_2\text{-}2)_4]$: A Model for the Reactive Structure of Organocuprates

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So far the cuprates, argentates, and aurates of the formula $M_2Li_2(C_6H_4X)_4(OEt_2)_n$ (X = 4-Me, $n = 2$;[1a] X = 2-Me_2NCH_2, $n = 0$;[1b] see Figure 1) are the only metal 1B–lithium species for which the structures *in solution* could be established by molecular weight measurements as well as ^1H, ^{13}C, ^6Li, and ^7Li NMR.[1,2] Observation of a $^1J(^{13}C(1)\text{–}^7Li)$ for these compounds and a $^1J(^{107,109}Ag\text{–}^{13}C(1))$ for $Ag_2Li_2(C_6H_4CH_2NMe_2\text{-}2)_4$ (**1b**) [1] established that (i) the metal 1B and the lithium atoms are part of the same cluster[3] and (ii) each of the aryl groups is three center-two electron bonded to a metal 1B–lithium atom pair. This information concerning the structure *in solution* is of prime importance for a better understanding of the mechanistic aspects of organocuprate reagents. The preferential coordination in **1** and **2**[3] of the N- and O-donor ligands to lithium rather than to the 1B metal gives credence to the belief that the lithium atoms are the anchoring sites of the α,β-unsaturated ketones (via O) in the conjugate addition reaction using organocuprates.[5]

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[2] The ^6Li and ^7Li NMR spectra of $Ag_2Li_2(C_6H_4CH_2NMe_2\text{-}2)_4$ in benzene-d_6 showed a triplet with a 1/2/1 intensity ratio (δ Li -0.10, $LiCl/D_2O$ external reference) due to $^2J(^6Li\text{–}^{107,109}Ag) = -1.46$, and $^2J(^7Li\text{–}^{107,109}Ag) = 3.91$ Hz. Brevard, C.; Jastrzebski, J. T. B. H.; van Koten, G., unpuslished results.

[3] In more basic ethers (i.e., THF) or in the presence of the powerful terdentate ligand pentamethyldiethylenetriamine the neutral CuLi clusters are transformed into ionic species in which the Li and Cu atoms are part of different units, i.e., $Ph_6Cu_5Li\cdot 4THF$ consists of a homonuclear anionic $Ph_6Cu_5^-$ cluster and $Li(THF)_4^+$ cations.[4]

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