Nature of the transition state in gas phase S_N2 identity reactions: correlation between nucleophilicity and proton affinity

Einar Uggerud

Department of Chemistry, University of Oslo, PO Box 1033 Blindern, N-0315 Oslo, Norway.
E-mail: einar.uggerud@kjemi.uio.no

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The potential energy profiles of the cationic: $A + CH_3A^+ \rightarrow {}^+ACH_3 + A$ ($A = NH_3, H_2O, HF$), and anionic: $A^- + CH_3A \rightarrow ACH_3 + A^-$ ($A^- = NH_2^-, OH^-, F^-$) S_N2 reactions were obtained using quantum chemical methods [MP2, G2, CCSD(T)]. A linear rate–energy relationship in the form of a correlation between the critical energy, ΔE^{diff}, and the proton affinity of A was found within subgroups of similar nucleophiles (NH_3, H_2O, HF; NH_2^-, OH^-, F^- ; F^-, Cl^-, Br^-, I^-). The analysis shows that the different susceptibility for each class is due to properties of the transition structures alone, and not of the reactants.

Introduction

The vast body of information generated by scientific research has to be systematized and linked to known phenomena in order to be comprehended by the human mind. In chemistry there is a long tradition of understanding the properties of stable molecules in terms of periodic trends and structural features. Likewise, insight into chemical reactivity is provided in terms of linear rate–energy relationships[1] (Brønsted relationship,[2] Hammet equation,[3] Swain–Scott equation[4]). Such relationships result from systematic trends in the different susceptibilities of the energies of the reactant and the transition structure of a reaction to a given structural variation.

A complication often arises when a reaction occurs in solution, because it may be difficult to distinguish clearly between the intrinsic properties of the key molecules of the system (reactant, transition state), and the modulating effect of the medium. It has been demonstrated that a successful approach to this problem is to undertake studies in the gas phase to complement studies in solution. The results of comparative studies of this kind are very valuable, because they lead to a more solid foundation of the theory. In this way previously established models and explanations, sometimes of dubious and *ad hoc* character, may be revised and brought into better accord with the real underlying causes.

The elementary S_N2 reaction [eqn. (1)] is a typical

$$X + RY \rightarrow RX + Y \qquad (1)$$

example.[5–10] It is probably the most widely studied reaction in physical organic chemistry, and it is well known to all chemists because it is described in great detail in all introductory textbooks of organic chemistry.

In the S_N2 mechanism the nucleophile (X)[11] attacks from the end opposite to that of the nucleofuge (leaving group, Y)[12] and the new bond is formed gradually as the old bond is broken. The rate determining step is bimolecular, there is no intermediate carbocation, a single transition state is passed, and the mechanism explains why inversion of configuration around the central carbon atom (Walden inversion) is usually observed when the reaction follows this mechanism.

The S_N2 reaction has also been studied thoroughly in the gas phase. Interestingly, most of the published literature is concerned with the anionic subclass [eqn. (2)], propelled by

$$X^- + RY \rightarrow XR + Y^- \qquad (2)$$

pioneering work in the field of gas phase negative ion–molecule chemistry.[13–22] On the other hand, the cationic subclass [eqn. (3)]

$$X + RY^+ \rightarrow {}^+XR + Y \qquad (3)$$

has received less attention, although some gas phase studies exist.[23–34] Cationic S_N2 reactions are important in solution chemistry, especially in connection with acid catalysis.

A very important contribution to our current understanding of gas phase anionic S_N2 reactivity stems from theoretical studies. Through the last two decades more than 200 theoretical papers have appeared in the chemical literature.[10,35–45] A relatively limited number of substrates (R groups), nucleophiles (X^-) and nucleofuges (Y^-) have been studied. For a given R group it has been shown that reactivity may be understood by consideration of identity reactions[46] (where $X = Y$). The activation energies of reactions with $X \neq Y$ may be deduced from the activation energies of the identity reactions of X and Y, and the reaction exothermicity, by using Marcus theory.[36,47–49] Even solvent effects have been treated theoretically with success.[50] Cationic reactions have also been studied, and a limited number of papers have been published.[31,34,51–54]

This paper is devoted to some simple gas phase S_N2 reactions—both anionic and cationic—and quantum chemical methods will be used to generate reaction potential energy profiles, structural data, and energetical parameters. Because neutral nucleophiles and nucleofuges are poorer electron donors than anionic nucleophiles, it will be of particular interest to look for similarities and differences in the two different classes of reactions. The overall purpose is to obtain insight into the factors which govern reactivity. The reactions shown in eqn. (4) and (5) were studied.

$$A + CH_3A^+ \rightarrow {}^+ACH_3 + A \; (A = NH_3, H_2O, HF) \qquad (4)$$

$$A^- + CH_3A \rightarrow ACH_3 + A^- \; (A^- = NH_2^-, OH^-, F^-) \qquad (5)$$

Methods

Quantum chemical calculations were carried out using the program system GAUSSIAN 94.[55] The methods used were Møller–Plesset perturbation theory to second order (MP2)[56] with the 6-31G(d,p) basis set,[57] and the compound G2 method.[58] In addition, coupled cluster theory calculations of the type CCSD(T)/6-311+G(2df,2pd)[59] at the MP2/6-31G(d,p)

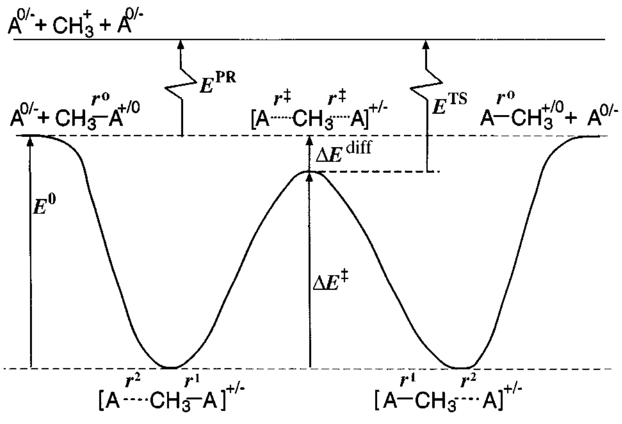

Fig. 1 Schematic potential energy diagram for an identity S_N2 reaction. The illustration includes both cationic and anionic reactions. The signs (0, + or −) designate the charge of the species. The sign before the slash (/) refers to the cationic case, while that behind refers to the anionic.

optimized geometries were performed for all species included in the study of the carbocationic reactions.

All relevant critical points (reactants, transition structures, intermediates and products) of the potential energy surface were characterized by complete optimization of the molecular geometries [MP2/6-31G(d,p)]. Harmonic frequencies were obtained by diagonalizing the mass-weighed Cartesian force constant matrix, calculated from the analytical second derivatives of the total energy (the Hessian). Harmonic frequencies obtained in this manner were used to calculate the zero point vibrational energies (zpve). Total energies were calculated by including the MP2/6-31G(d,p) zero point vibrational energies scaled by a factor of 0.967. For the G2 method the built-in scale factor was used.

Proton affinities [see eqn. (9) below for definition] were calculated by adding (5/2) RT (with $T = 298$ K) to the energy difference between A and AH^+ for MP2 and CCSD(T), and to the 298 K enthalpy differences for G2. The methyl cation affinities were calculated directly in accordance with eqn. (10) using the 298 K energy/enthalpy differences.

Results and discussion

We will first concentrate on the three cationic identity S_N2 reactions [eqn. (6)–(8)]. Fig. 1 shows a general reaction

$$H_3N + CH_3NH_3^+ \rightarrow {}^+H_3NCH_3 + NH_3 \qquad (6)$$

$$H_2O + CH_3OH_2^+ \rightarrow {}^+H_2OCH_3 + OH_2 \qquad (7)$$

$$HF + CH_3FH^+ \rightarrow {}^+HFCH_3 + FH \qquad (8)$$

potential energy diagram, which demonstrates schematically how the reactions occur. It also defines some key energy parameters, which will be referred to in the following discussion. The cationic S_N2 reaction has the same characteristics as its anionic counterpart. Briefly described, it occurs in three steps.

(i) Formation of the reactant complex, $A\cdots CH_3A^+$. This complex is relatively weakly bonded, and the interaction within the ion–neutral complex is mainly electrostatic. It should be realized that the global minimum of these potential energy surfaces corresponds to complexes of the type $CH_3A^+\cdots A$, wherein the interaction between the neutral and ionic parts is due to a hydrogen bond. A complete dynamic treatment of collisions between A and CH_3A^+ should of course incorporate the hydrogen bonded species, but because the concern of this paper is the basic energetics of the chemical transformation, only species directly *en route* to the transition structure have been considered.

(ii) Passage through the transition structure, $[A\cdots CH_3^+\cdots A]$.

(iii) Formation of the product complex, $ACH_3^+\cdots A$, which is the mirror image of the reactant complex. Dissociation of this complex leads to the products.

Energy and structural data of the reactions are presented in Table 1. Supplementary data can be obtained from the author upon request. The table also includes proton affinities (PA) of the nucleophiles (A) [eqn. (9)] and also their methyl cation affinities (MCA).

$$A + H^+ \rightarrow AH^+ \quad PA = -\Delta H^\circ \qquad (9)$$

$$A + CH_3^+ \rightarrow CH_3A^+ \quad MCA = -\Delta H^\circ \qquad (10)$$

Our results are in good agreement with previous calculations of reaction (7) ($A = H_2O$).[51,54] The results of the G2 and CCSD(T)/6-311+G(2df,2pd) calculations give very similar results, as can be inferred from Table 1.

From the data we see that the barrier for the actual chemical transformation—represented either by the activation energy, $\Delta E^‡$, measured from the intermediate, or the critical energy, ΔE^{diff}, measured from the reactants—increases in the order $HF < H_2O < NH_3$. This trend parallels the order of the proton affinities and methyl cation affinities of the three nucleophiles/nucleofuges. We also notice that the curvature of the potential energy surface in the direction of the reaction co-ordinate—measured by the imaginary frequency of vibration (or more precisely, the corresponding force constant)—increases in the same manner. In addition to this there is a correlation between the increase in the C–A bond length upon going from reactants to transition structure, expressed by the difference $r^‡ - r^\circ$, and the critical energy.

The three identity anionic S_N2 reactions [eqn. (11)–(13)] were

$$H_2N^- + CH_3NH_2 \rightarrow H_2NCH_3 + NH_2^- \qquad (11)$$

$$HO^- + CH_3OH \rightarrow HOCH_3 + OH^- \qquad (12)$$

$$F^- + CH_3FH^+ \rightarrow FCH_3 + F^- \qquad (13)$$

also investigated. In this case we did not perform CCSD(T) calculations, but from the cationic reactions we had reason to expect that the G2 results would be fully appropriate. The results are given in Table 1. Also for these reactions Fig. 1 is applicable, and the reaction mechanism includes the same steps as the cationic counterpart. The only exception is reaction (11). No minimum corresponding to a species of the type $H_2N^-\cdots CH_3NH_2$ could be found. The only minimum is the hydrogen bonded species $CH_3NH_2\cdots NH_2^-$. The minimum energy path which leads from the transition structure goes directly from this species to an identical structure where the two NH_2 entities are interchanged. This was deduced from a reaction path following calculation [MP2/6-31G(d,p)]. Starting from $CH_3NH_2\cdots NH_2^-$ the NH_2^- unit has to swing around and perform a space walk in order to enter the methyl carbon from the back side. Apart from this detail our results appear to be in qualitative accordance with the literature.[35,36,38–40]

Again, we notice that the barrier heights increase with increasing proton and methyl cation affinity in the order $F^- < OH^- < NH_2^-$. Due to the absence of a stable $H_2N\cdots CH_3NH_2$ species, only the ΔE^{diff} parameter applies in this case.

The properties of the symmetrical transition structures, as a function of the nucleophile A, will be the central theme of this discussion. According to the normal definition, nucleophilicity is the relative ability of a molecule to donate an electron pair to assist displacement of a nucleofuge (leaving group). A quantitative measure of this is obtained from linear free energy relationships determined from the rates of substitution in the series of reactions, A + R–B→R–A + B, where the nucleofuge

Table 1 Energy data

Nucleophile	Method	PA[a]	MCA[b]	$E^{\circ c}$	$\Delta E^{\mathrm{diff}\,c}$	$\Delta E^{\ddagger c}$	$E^{\mathrm{TS}\,d}$	$\nu^{\ddagger}$/cm$^{-1\,e}$	r°/Å^{c}	$r^{\ddagger}$/Å^{c}
		Energy/kJ mol^{-1}								
NH_3	MP2	876	468	43	86	43	419	614	1.510	2.002
	G2	854	438	34	90	56	374			
	CCSD(T)	859	437	37	89	52	379			
	exp.	854	441							
H_2O	MP2	704	296	50	43	−8	303	499	1.518	1.953
	G2	689	277	41	40	−1	270			
	CCSD(T)	695	275	41	46	5	264			
	exp.	691	279							
HF	MP2	505	154	50	6	−44	192	265	1.606	1.968
	G2	486	123	43	9	−34	152			
	CCSD(T)	496	122	42	7	−35	150			
	exp.	484	125							
NH_2^-	MP2	1821	1371	—	—	83	1282	613	1.465	1.993
	G2	1691	1227	—	—	118	1101			
	exp.	1691	1234							
OH^-	MP2	1768	1309	73	89	16	1287	582	1.424	1.883
	G2	1633	1154	26	85	59	1088			
	exp.	1634	1159							
F^-	MP2	1705	1251	107	46	−61	1311	511	1.392	1.781
	G2	1554	1078	55	49	−6	1077			
	exp.	1554	1080							

[a] Proton affinity, eqn. (9). [b] Methyl cation affinity, eqn. (10). [c] See Fig. 1 for definition of this quantity. [d] See eqn. (14) for definition. [e] Imaginary frequency of vibration of reaction co-ordinate. Experimental data were taken from ref. 63 and 64.

B is kept constant. Likewise, the nucleofugacity of a molecule is the relative ability to accept an electron pair to assist placement of a nucleophile, and it can be measured accordingly. In an identity S_N2 reaction these two properties balance, and the barrier height obtained is the key figure, which describes them both. In the introduction we mentioned that Marcus theory has been applied successfully to obtain barriers for reactions of the type A + R–B→R–A + B, when the barriers of the two identity reactions A + R–A→R–A + A and B + R–B→R–B + B are known. The only additional parameter is the potential energy change of the reaction.

To express the relationship between the relevant energetic parameters and the barrier height we need a common point of reference (Fig. 1). The energy of the separated units A + CH_3^+ + A is the natural choice (please note that the Lewis base A may either be neutral or have one negative charge). In this way the relative potential energy of a symmetrical transition structure may be examined by reference to the thought reaction in eqn. (14). With this reference the energy of the reactants is

$$\mathrm{A} + \mathrm{CH_3}^+ + \mathrm{A} \rightarrow [\mathrm{A}\cdots\mathrm{CH_3}^+\cdots\mathrm{A}], \quad -E^{\mathrm{TS}} \qquad (14)$$

given by eqn. (15). By comparison with eqn. (10) we observe that

$$\mathrm{A} + \mathrm{CH_3}^+ + \mathrm{A} \rightarrow [\mathrm{A} + \mathrm{CH_3A}^+] \quad -E^{\mathrm{PR}} \qquad (15)$$

E^{PR} = MCA. The difference in energy between the TS and the reactants is therefore given by $\Delta E^{\mathrm{diff}} = E^{\mathrm{PR}} - E^{\mathrm{TS}} = \mathrm{MCA} - E^{\mathrm{TS}}$.

During the hypothetical reaction illustrated in eqn. (14) one constraint has been imposed on the system; namely that the lengths, r, of the A···C and C···A bonds are set to be equal, and the A groups are placed one on each face of the planar methyl cation. Starting from infinite separation, $r = \infty$, the potential energy of the combined system decreases until the transition structure geometry is reached. The TS is seen to constitute an energy minimum with the restrictions given. It turns out that a very interesting linear energy relationship exists between the interactions in this [A···CH_3^+···A] species and in the CH_3A^+ molecule. This is shown in Fig. 2. The three cationic reactions (6)–(8) all lie on a straight line in a plot of E^{TS}(A) *versus* the proton affinity of A (the lower left part of Fig. 2). Fig. 2 also shows the linear relationship between the methyl cation affinity and the proton affinity of a species. The MCA/PA relationship is well established in the literature,[60–62] but the E^{TS}/PA relationship is novel. As a consequence, there is

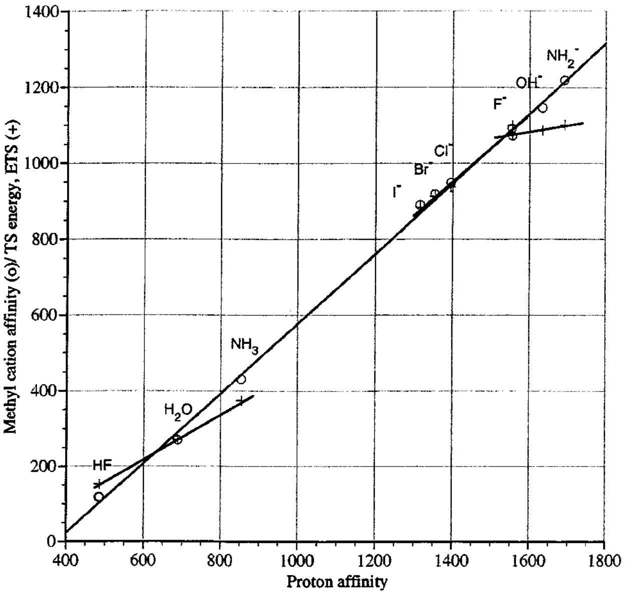

Fig. 2 Plot showing the correlation between methyl cation affinities (open circles) and proton affinities, and relative transition structure energies, E_{TS} (crosses) and proton affinities. For the nucleophiles HF, H_2O, NH_3, F^-, OH^- and NH_2^- data were taken from this work (G2 values), and for I^-, Br^-, Cl^- and F^- data were taken from ref. 53 (G2 values), supplemented with experimental data from ref. 63 and 64. There are two entries for F^-. The slightly smaller MCA and E^{TS} values are from this work.

a linear relationship between E^{TS} and MCA. The first indication of a E^{TS}/PA relationship came from a recent study[49] we performed for cluster models of reaction (7). It turned out that the activation energies for S_N2 reactions of protonated methanol microsolvated by water increased linearly with the proton affinity of the relevant water cluster, $(H_2O)_n$. We would like to mention that Shi and Boyd have found a related linear relationship between $\Delta E^{\ddagger}$ and the electronegativity of the A group in identity anionic S_N2 reactions.[39]

We also notice a corresponding linear energy relationship for the anionic reactions (11)–(13) (Fig. 2, upper right part). In this case the E^{TS} line is less steep. Fig. 2 also includes computational results for (Cl^-, Br^- and I^-) of Glukhovtsev *et al.*[53] It was necessary to include literature experimental bond dissociation energies[63,64] to supplement the data of Glukhovtsev *et al.* Within the sub-class $A = F^-, Cl^-, Br^-, I^-$ the E^{TS} and MCA values are almost identical, and ΔE^{diff} is therefore close to zero. Throughout the whole series HF–NH_2^-, corresponding to a span in proton affinities from 450 to 1700 kJ mol^{-1}, the almost perfect straight line obtained for the MCA *versus* PA plot is quite noteworthy.

The transition structures $[A\cdots CH_3\cdots A]^{+/-}$ correspond to situations where a central methyl cation is complexed by two identical A groups. Whether the sum of the two interactions in the TS is equal to, slightly smaller than, or slightly bigger than the single interaction in the corresponding $CH_3A^{+/0}$ species determines the magnitude of the barrier, ΔE^{diff}. Within each class of A groups (HF–NH_3; I^-–F^-; F^-–NH_2^-) the susceptibility of the transition structure energy, E^{TS}, to the proton affinity is the same. The fact that it is not the same for all the classes is interesting. A number of small stereochemical and electronic factors are probably contributing. As already mentioned, Shi and Boyd found a linear relationship between $\Delta E^{\ddagger}$ and the electronegativity of the A group.[39] They found that the susceptibility was different for the different classes. From a quite detailed analysis of the properties of the electron densities of the stable CH_3A molecules they attributed the differences to different hybridization factors for each class. Shaik and Pross have suggested a similar dependency, using an alternative approach.[65,66] The explanations by Shi and Boyd and Shaik and Pross are both very clear-sighted and highly valuable. However, the strength of our analysis is that the plot of Fig. 2 shows that the difference in the susceptibilities within each class is due to the transition structures alone. The universal MCA/PA relationship excludes the possibility that the energies of the reactants should be of any importance. The nature of the interaction between the two A groups within $[A\cdots CH_3\cdots A]^{+/-}$ is probably the key. In addition to the electron donating capacity of A, the repulsive character of the $A\cdots A$ interaction determines the height of the barrier. It is easy to understand that this property may be different for different classes of A groups, depending upon charge and effective atomic radii. With more data it will hopefully be possible to propose an equation for the barrier of any S_N2 reaction, which incorporates only one parameter in addition to the proton affinity.

The existence of linear rate–energy relationships for S_N2 reactions can be dated back to an influential publication by Swain and Scott.[4] They introduced the concept of nucleophilicity, n, by defining a linear relationship of the type in eqn. (16). In this equation k_o refers to the rate of a standard

$$\log (k/k_o) = ns \qquad (16)$$

reaction, and k is the rate of the reaction of the nucleophile under consideration. The parameter s is the sensitivity of the given substrate. They studied the displacement of bromide and other nucleofuges using different nucleophiles and substrates. Their standard reaction was that in eqn. (17).

$$A^- + CH_3Br \rightarrow ACH_3 + Br^- \qquad (17)$$

One problem with the Swain–Scott relationship is that it is not universal. It is however of great significance because it offers a unique insight into the nature of the S_N2 reaction, although it fails to correlate the concept of nucleophilicity to that of basicity. Due to specific and general solvent effects the Brønsted basicity and the nucleophilicity of a given nucleophile may be affected differently, often in an unpredictable manner, in different solvents. More refined multi-parameter relationships based on the concept of hard and soft bases and similar ideas have been more successful, but are also of limited validity.[67–69] More recently, the substantial work of Ritchie and co-workers on recombination reactions between carbocations and nucleophiles in solution [eqn. (18)] has shown that in many cases there

$$A + R^+ \rightarrow RA \qquad (18)$$

is a linear relationship between the rate and the equilibrium constant, at least in reactions which appear to be S_N1.[70] It is also of relevance to mention that McManus has showed that in some cases there is a good correlation between gas phase proton affinities and solvent S_N2 nucleophilicities.[71]

Despite all these insightful approaches to understand the central features of S_N2 reactions, a more generally valid approach has to be taken to bring theory to a more quantitative level. The data presented here show that a one-parameter general rate–energy relationship should not be expected for S_N2 reactions, neither in the gas phase nor in solution. However, within a class of chemically related nucleophiles such a relationship exists. This is promising, because it may lead to a generally valid and simple two-parameter expression, as discussed above. The historical influence of the Swain–Scott equation, and their concept of nucleophilicity in particular, is highly appreciated. The increasing number of gas phase studies of identity reactions does, however, suggest a revision of strategy for how S_N2 reactions should be understood. The Marcus equation relationship for reactions with different entering and leaving groups implies that the exothermicity of a reaction to a large extent controls the barrier height. Instead it would be much more natural to relate the intrinsic property of nucleophilicity to the barrier height of identity reactions. Pellerite and Brauman have therefore suggested this.[72,73] Based on the above discussion our suggestion is different. In order to avoid confusion, we suggest that the terms nucleophilicity and nucleofugacity can be substituted by the single term, nucleoaffinity,[74] which we will define by the energy difference, $E^{TS}(A)$. Before this can be done we think that more evidence is needed, so many experimental and theoretical studies remain to be conducted. A wider range of nucleophiles and nucleofuges need to be investigated systematically and uniformly, using for example the G2 method. The effect of the substrate, R, is as of yet poorly understood—the idea of steric hindrance is central in the traditional interpretation of reactions on substituted carbon centres—but our recent work on reactions between water and protonated alcohols has challenged the traditional view of this concept.[34] For this reason a great variety of substrates need to be examined as well.

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74 Nucleoaffinity, from lat. *nucleus*, dim. of *nux nucis* nut, kernel and lat. *affinitas*, related, lit. bordering on. The ability of a nucleofuge/nucleophile to accommodate nucleophilic displacement in the identity (narcissistic) reaction $A + CH_3A \rightarrow CH_3A + A$. Defined as the negative enthalpy change of the hypothetical reaction $A + CH_3^+ + A \rightarrow [A \cdots CH_3^+ \cdots A]$. The latter species it the transition structure of the reaction (definition suggested here).

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