The S_N2 reaction and its relationship with the Walden inversion, the Finkelstein and Menshutkin reactions together with theoretical calculations for the Finkelstein reaction

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Abstract

This communication gives an overview of the relationships between four reactions that although related were not always perceived as such: S_N2 , Walden, Finkelstein, and Menshutkin. Binary interactions (S_N2 & Walden, S_N2 & Menshutkin, S_N2 & Finkelstein, Walden & Menshutkin, Walden & Finkelstein, Menshutkin & Finkelstein) were reported. Carbon, silicon, nitrogen, and phosphorus as central atoms and fluorides, chlorides, bromides, and iodides as lateral atoms were considered. Theoretical calculations provide Gibbs free energies that were analyzed with linear models to obtain the halide contributions. The M06-2x DFT computational method and the 6-311++G(d,p) basis set have been used for all atoms except for iodine where the effective core potential def2-TZVP basis set was used. Concerning the central atom pairs, carbon/silicon vs. nitrogen/phosphorus, we reported here for the first time that the effect of valence expansion was known for Si but not for P. Concerning the lateral halogen atoms, some empirical models including the interaction between F and I as entering and leaving groups explain the Gibbs free energies.

Keywords S_N2 · Walden · Finkelstein · Menshutkin · Atom effects · DFT calculations

Introduction

There are four well-known reactions that are mutually related, the S_N2 reaction, the Walden inversion, the Finkelstein reaction, and the Menshutkin reaction, and their two-to-two relationships are often reported, but never their whole set (Fig. 1).

The IUPAC only reports a paper on the steric and electronic effects in the S_N2 reactions [1] and a definition of the Walden inversion [2].

The four reactions

Here are the four definitions with some references that report both experimental and theoretical results:

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S_N2

Substitution nucleophilic bimolecular reaction involves a nucleophilic substitution reaction mechanism where one bond is broken and one bond is formed synchronously [3–11]. The standard case involves a central carbon atom ($S_N2@C$) [12], but it was soon extended to a central silicon atom ($S_N2@Si$), but in this case, the TS becomes a minimum, single-well, due to silicon

Fig. 1 Binary relationships between the four properties

hypervalency [12, 13]. In the simplest case, for any halogen atoms, the reactions follow different pathways (Scheme 1).

Scheme 1 The S_N2 reaction

Walden inversion

The Walden inversion is the inversion of a chiral center in a molecule in a chemical reaction. In an S_N2 reaction, the reaction occurs in a tetrahedral carbon atom (Scheme 2) [14–17].

Scheme 2 An example of Walden inversion

Finkelstein reaction

The Finkelstein reaction is an S_N2 reaction that involves the exchange of one halogen for another (Scheme 3) [18, 19].

Scheme 3 The Finkelstein reaction (X ≠ Y)

Menshutkin reaction

The Menshutkin reaction converts a tertiary amine into a quaternary ammonium salt by reaction with an alkyl halide. We will slightly modify this definition to involve a type S_N2@N⁺ reaction where the central atom is a quaternary N atom [20–24], and, in a further step, a quaternary P atom, S_N2@P⁺ (Scheme 4) [25–27].

Scheme 4 An extension of the Menshutkin reaction. The X atom is Cl, Br or I. Note that in the case of phosphonium the minimum is a neutral trigonal bipyramid of D_{3h} symmetry

A comment about the X[−] + H₃NX⁺ or XNH₃⁺+X[−] salt: due to proton transfer, it can exist as a H₂XN + HX complex that depending on the nature of X and on the substituents on the nitrogen atom will be more or less stable than the salt. This continuum has been studied by Legon in the gas phase by rotational spectroscopy [28, 29], by Limbach in solution by NMR [30–32], by Tokmakoff in water solution by femtosecond two-dimensional IR [33], by Nangia in the solid-state X-ray photoelectron spectroscopy (XPS) [34], and in the solid state by crystallography (this is related to the salt/co-crystal continuum) [35–37] and theoretically by Del Bene [38–41].

The binary interactions

S_N2 & Walden

This is the most obvious link and, for this reason, where there are the largest number of references. Barone, Adamo et al. consider the Walden inversion the prototypical S_N2 reaction [42]. Using the same model that of Scheme 2, Bogdanov and McMahon using mass spectrometry and B3LYP/6-311+G(3df)//B3LYP/6-311+G(d) calculations prove that the S_N2 reactions are initiated via a back-side attack [43] (for some authors, the Walden inversion corresponds to the back-side attack in a S_N2 reaction). Grabowski reported MP2/aug-cc-pVTZ calculations of S_N2/Walden processes with central atoms being C, Si, and Ge [44]. High-level calculations [AE-MP2, AE-CCSD, and AE-CCSD(T), where AE denotes all-electron] we used to study the F[−] + CH₃F reaction [45]. The same authors reported the double-inversion mechanism of the F[−] + CH₃Cl reaction [46] (see also [47]). Chlorine isotope effects were calculated theoretically [UCCSD(T)-F12a/aug-cc-pVTZ] by Zhao, Zhang et al. [48]. Hamlin, Swart, and Bickelhaupt carried out a very general study of the S_N2 reactions covering aspects such as nucleophilicity, leaving groups, central atoms and solvent effects reported as a minireview [49].

S_N2 & Menshutkin

The Menshutkin reaction (H₃N + CH₃Cl → H₃NCH₃⁺ + Cl[−]) is the prototype of S_N2 reactions of type II, where the reactants are neutral, as opposed to the usual type I S_N2 reactions where

both the nucleophile and leaving group bear negative charges ($\text{Cl}^- + \text{CH}_3\text{Cl} \rightarrow \text{ClCH}_3 + \text{Cl}^-$). The $\text{Cl}^- + \text{CH}_3\text{Cl} \rightarrow \text{ClCH}_3 + \text{Cl}^-$ reaction was studied using a valence bond method coupled to a polarized continuum model, VBPCM [50]. Related studies but on more complex reactions ($\text{H}_3\text{N} + \text{ArCH}_2\text{Br}$) were studied using the through-space/bond (TS/TB) interaction analysis [51]. Both type I ($\text{S}_{\text{N}}2$) and type II (Menshutkin) reactions were compared using an ab initio quantum mechanical/molecular mechanic approach [52].

$\text{S}_{\text{N}}2$ & Finkelstein

Although the Finkelstein reaction is a particular case of the $\text{S}_{\text{N}}2$ type I, there is only a publication where these two terms came

together [53]. Other examples such those reported earlier [46, 47] belong also to this group but the Finkelstein name was not used.

Walden & Menshutkin

Here, also we have found only one work where both these terms were cited. Shaik et al. predicted that external electric fields (EEFs) catalyze the front-side nucleophilic displacement reaction, thus violating the Walden inversion paradigm (Scheme 5). Besides this study also demonstrates that oriented EEFs will act as catalysts of the Menshutkin reaction [54].

Scheme 5 Back-side attack consistent with the Walden inversion

Walden & Finkelstein

The relationship has been established from old [55], but only recently [56] the much-studied $\text{Cl}^- + \text{CH}_3\text{Cl} \rightarrow \text{ClCH}_3 + \text{Cl}^-$ reaction was classified both as a prototypical symmetric $\text{S}_{\text{N}}2$ reaction and as a model of Walden inversion.

Menshutkin & Finkelstein

The already cited article of Yamataka [49] not only relates $\text{S}_{\text{N}}2$ & Finkelstein but also Menshutkin.

Computational details

The systems have been optimized using the M06-2x DFT computational method [57] and the 6-311++G(d,p) basis set [58, 59]. The effective core potential def2-TZVP basis set [60]

has been used for iodine. Frequency calculations have been performed to verify that the geometries obtained correspond to energetic minima or true transition states (zero and one imaginary frequencies, respectively) and to obtain the thermodynamic parameters. These calculations have been carried out with the Gaussian-16 program [61].

Results and discussion

Central atom comparisons

We will discuss the comparative behavior of the C, N, Si, and P as central atoms.

The left part of Scheme 6 assumes that the four $\text{S}_{\text{N}}2$ reactions are identical, and its right side shows that in both Si and P^+ , the reaction stops at the pentacoordinated structure, an anion for silicon and a neutral molecule for phosphorus.

Scheme 6 The four $\text{S}_{\text{N}}2$ reactions

This was well known for silicon [12, 13], but with P^+ , this situation has not been reported before (the Menshutkin examples stop at the quaternary salt [25–27]). The transformation of tetravalent phosphonium salts into pentavalent phosphoranes (right side, bottom equation) is a common reaction in phosphorus chemistry [62, 63]. The barrier for the $S_N2@C$ is 43.7 $\text{kJ}\cdot\text{mol}^{-1}$ [64] and for $S_N2@N^+$ is 33.4 $\text{kJ}\cdot\text{mol}^{-1}$; thus, a moderate decrease of the barrier was calculated (10.3 $\text{kJ}\cdot\text{mol}^{-1}$).

The structure of dibromo- λ^5 -phosphane, $\text{Br}-\text{PH}_3-\text{Br}$ trigonal bipyramidal (Fig. 2), differs from that determined by Legon [65] and calculated by Kraka and Cremer [66], $\text{H}_3\text{P}\cdots\text{Br}-\text{Br}$, a halogen-bonded complex, although both are minima (no imaginary frequencies). We have reported in a previous work that the P(V) derivatives are much more stable than the P(III) derivatives, although the last ones are stabilized by an halogen bond [67]. We have calculated the difference in energy of the two isomers of Fig. 2 resulting in the P(V) structure being 73 $\text{kJ}\cdot\text{mol}^{-1}$ more stable than the P(III) complex. The

other complexes $\text{X}-\text{PH}_3-\text{X}$ ($\text{X} = \text{F}, \text{Cl}, \text{I}$) are also minima. The other similar complexes $\text{X}-\text{PH}_3-\text{X}$ ($\text{X} = \text{F}, \text{Cl}$, and I) are also minima.

Fig. 2 The optimized geometry of $\text{Br}-\text{PH}_3-\text{Br}$ trigonal bipyramidal

Halogen atoms comparisons

We have calculated the exothermicity of the following six equilibria (Scheme 7), all of them are $S_N2@C$:

Scheme 7 Replacement of a halogen by another halogen

The ΔG calculated values of this work and some experimental literature values, all of them in $\text{kJ}\cdot\text{mol}^{-1}$, are reported in Table 1. Literature data for equations 1, 2, and 3 are calculated ΔH values. Truhlar values for equations 4, 5, and 6 are ΔE values calculated from ΔH and harmonic frequencies [71].

Our calculated values are proportional to the literature values:

$$\begin{aligned}
 \text{Lit.} &= (4.7 \pm 1.7) + (1.07 \pm 0.02) \Delta G, n = 6, R^2 \\
 &= 0.999
 \end{aligned} \quad (1)$$

A multi regression analysis of the data of Table 1 where the dependent variables are ΔG or Lit. and the independent

variables F, Cl, and Br (I is the reference) lead to a series of equations where the coefficients of the halogens are their individual contributions. For a more complete discussion of the use of Free-Wilson or presence-absence matrices, see [74–80].

$$\begin{aligned}
 \text{From } \Delta G : \text{F} &= (4.4 \pm 2.7), \text{Cl} = -(118.8 \pm 2.3), \text{Br} \\
 &= -(144.6 \pm 3.3), \text{I} \\
 &= -(159.8 \pm 4.5) \text{ kJ} \cdot \text{mol}^{-1}, R^2 \\
 &= 0.999, \text{RMS} = 2.7 \text{ kJ} \cdot \text{mol}^{-1}
 \end{aligned} \quad (2)$$

Table 1 Number of total admissions, average daily admission, average length of stay, and readmissions from March to October in 2019 and 2020

Calc. ΔG	Lit.	Lit.	Lit.	Scheme 7	F	Cl	Br	I
123.6	134 [68]	ΔH	Calc.	1	1	−1	0	0
150.4	168 [69]	ΔH	Calc.	2	1	0	−1	0
162.3	178 [70]	ΔH	Calc.	3	1	0	0	−1
28.4	34 [71]	ΔE	Exp.	4	0	1	−1	0
47.7	58 [71]	ΔE	Exp.	5	0	1	0	−1
19.1	25 [71]	ΔE	Exp.	6	0	0	1	−1
	Electronegativity [72]			---	4.0	3.0	2.8	2.5
	Ionization energy ($\text{kJ}\cdot\text{mol}^{-1}$) [73]			---	1681	1251	1140	1008

$$\begin{aligned}
 \text{From Lit. : } F &= (7.5 \pm 5.0), \text{Cl} = -(126.8 \pm 4.3), \text{Br} \\
 &= -(156.8 \pm 6.1), \text{I} \\
 &= -(174.0 \pm 8.2) \text{ kJ} \cdot \text{mol}^{-1}, R^2 \\
 &= 0.998, \text{RMS} = 5.0 \text{ kJ} \cdot \text{mol}^{-1}
 \end{aligned} \quad (3)$$

If we impose that the intercept should be = 0, *i.e.* $F = 0.0$, then:

$$\begin{aligned}
 \text{From } \Delta G : F &= 0.0, \text{Cl} = -(121.0 \pm 2.4), \text{Br} \\
 &= -(149.0 \pm 2.4), \text{I} \\
 &= -(166.4 \pm 2.4) \text{ kJ} \cdot \text{mol}^{-1}, R^2 \\
 &= 0.999, \text{RMS} = 3.4 \text{ kJ} \cdot \text{mol}^{-1}
 \end{aligned} \quad (4)$$

$$\begin{aligned}
 \text{From Lit. : } F &= 0.0, \text{Cl} = -(130.5 \pm 4.2), \text{Br} \\
 &= -(164.2 \pm 4.2), \text{I} \\
 &= -(185.2 \pm 4.2) \text{ kJ} \cdot \text{mol}^{-1}, R^2 \\
 &= 0.999, \text{RMS} = 5.9 \text{ kJ} \cdot \text{mol}^{-1}
 \end{aligned} \quad (5)$$

Equations (2) and (3) assume that there is no interaction between both halogens in the complexes. If the most obvious (F/I, the most different halogens) interaction was considered, then Eq. (6) was obtained:

$$\begin{aligned}
 \text{From } \Delta G : F &= 0, \text{Cl} = -(123.0 \pm 0.6), \text{Br} \\
 &= -(151.0 \pm 0.6), \text{I} \\
 &= -(170.4 \pm 0.7), \text{interaction F/I} \\
 &= -(8.1 \pm 1.0) \text{ kJ} \cdot \text{mol}^{-1}, R^2 = 1.000, \text{RMS} \\
 &= 0.7 \text{ kJ} \cdot \text{mol}^{-1}
 \end{aligned} \quad (6)$$

The coefficients of Eq. (6) are those that better fit with two properties of the halogen atoms, the electronegativity (relative scale) and the ionization energy ($\text{kJ} \cdot \text{mol}^{-1}$). With this last one we obtain:

$$\begin{aligned}
 \text{From } \Delta G : \text{Halogen values of eq.6} \\
 &+ (0.982 \pm 0.003) \text{ ionization energies, n} \\
 &= 4, R^2 = 1.000, \text{RMS} = 0.7 \text{ kJ} \cdot \text{mol}^{-1}
 \end{aligned} \quad (7)$$

$$\begin{aligned}
 \text{From Lit. : Halogen values of eq.6} \\
 &+ (1.081 \pm 0.003) \text{ ionization energies, n} \\
 &= 4, R^2 = 1.000, \text{RMS} = 1.6 \text{ kJ} \cdot \text{mol}^{-1}
 \end{aligned} \quad (8)$$

The very good quality of Eqs. (7) and (8) proves that our analysis of the energetic values of the six $\text{S}_{\text{N}}2$ reactions that lead to atomic contributions is justified.

Conclusions

After showing that four classical organic chemistry reactions are more related than it was previously believed a series of theoretical calculations analyze the energetic data. Concerning the central atom pairs, C/Si and N/P the effect of valence expansion was known for Si, but for P was reported here for the first time. Concerning the halogen atoms, some empirical models including the interaction between F and I as entering and leaving groups successfully explain the Gibbs free energies; the model coefficients are related to some fundamental properties as the electronegativity and the ionization energies.

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Code availability Not applicable.

Author contribution I.A. did the calculations. J.E. wrote the first draft of the article. Both authors have read and agreed to the published version of the manuscript.

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Declarations

Conflict of interest The authors declare no competing interests.

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