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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Received: 31 May 2021 / Accepted: 17 June 2021 / Published online: 31 July 2021
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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:

$S_N2$

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

\[
\begin{align*}
X^- + H\overset{\text{C}}{-\text{C}}{-\text{X}} & \rightarrow X\overset{\text{C}}{-\text{C}}{-\text{H}} + X^- \\
X^- + H\overset{\text{Si}}{-\text{Si}}{-\text{X}} & \rightarrow X\overset{\text{Si}}{-\text{Si}}{-\text{H}} + X-
\end{align*}
\]

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].

\[
\begin{align*}
\text{Br}^- + F\overset{\text{C}}{-\text{C}}{-\text{Br}} & \rightarrow \text{Br}\overset{\text{C}}{-\text{C}}{-\text{F}} + \text{Br}^- \\
\text{Cl}^{(R)} + H\overset{\text{C}}{-\text{C}}{-\text{Cl}} & \rightarrow \text{Cl}^{(S)} + H\overset{\text{C}}{-\text{C}}{-\text{Cl}}
\end{align*}
\]

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].

\[
\begin{align*}
X^- + H\overset{\text{C}}{-\text{C}}{-\text{Y}} & \rightarrow X\overset{\text{C}}{-\text{C}}{-\text{H}} + Y^-
\end{align*}
\]

Scheme 3 The Finkelstein reaction (\(X \neq Y\))

**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].

\[
\begin{align*}
X^- + H\overset{\text{N}}{-\text{N}}{-\text{X}} & \rightarrow X\overset{\text{N}}{-\text{N}}{-\text{H}} + X^- \\
X^- + H\overset{\text{P}}{-\text{P}}{-\text{X}} & \rightarrow X\overset{\text{P}}{-\text{P}}{-\text{H}} + X^-
\end{align*}
\]

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 \(X^- + H_2NX^+\) or \(XNH_3^++X^-\) salt: due to proton transfer, it can exist as a \(H_2XN + HX\) 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, 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, Bogданov 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 \(F^- + CH_3F\) reaction [45]. The same authors reported the double-inversion mechanism of the \(F^- + CH_3Cl\) 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 (\(H_3N + CH_3Cl \rightarrow H_3NCH_3^+ + Cl^-\)) 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 (Cl$^{-}$ + CH$_3$Cl → ClCH$_3$ + Cl$^{-}$). The Cl$^{-}$ + CH$_3$Cl → ClCH$_3$ + Cl$^{-}$ reaction was studied using a valence bond method coupled to a polarized continuum model, VBPCM [50]. Related studies but on more complex reactions (H$_3$N + ArCH$_2$Br) were studied using the through-space/bond (TS/TB) interaction analysis [51]. Both type I (SN$_2$) and type II (Menshutkin) reactions were compared using an ab initio quantum mechanical/molecular mechanic approach [52].

**SN$_2$ & Finkelstein**

Although the Finkelstein reaction is a particular case of the SN$_2$ 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].

**Menshutkin & Finkelstein**

The already cited article of Yamataka [49] not only relates SN$_2$ & 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 SN$_2$ 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.
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 kJ·mol^-1 [64] and for S_N2@N^+ is 33.4 kJ·mol^-1; thus, a moderate decrease of the barrier was calculated (10.3 kJ·mol^-1).

The structure of dibromo-λ^5-phosphane, Br_PH_3–Br trigonal bipyramidal (Fig. 2), differs from that determined by Legon [65] and calculated by Kraka and Cremer [66], H_3P···Br–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 kJ·mol^-1 more stable than the P(III) complex. The other complexes X_PH_3–X (X = F, Cl, I) are also minima. The other similar complexes X_PH_3–X (X = F, Cl, and I) are also minima.

### 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 |
|----------|------------------------------------------|
| 1 F^−→H_3CCl | Cl^−→H_3CF |
| 2 F^−→H_3CBr | Br^−→H_3CF |
| 3 F^−→H_3Cl | I^−→H_3CF |
| 4 Cl^−→H_3CBr | Br^−→H_3Cl |
| 5 Cl^−→H_3Cl | I^−→H_3Cl |
| 6 Br^−→H_3Cl | I^−→H_3Br |

The ΔG calculated values of this work and some experimental literature values, all of them in kJ·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:

\[
\text{Lit.} = (4.7 \pm 1.7) + (1.07 \pm 0.02) \Delta G, n = 6, R^2 = 0.999
\]

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].

From ΔG: F = (4.4 ± 2.7), Cl = -(118.8 ± 2.3), Br

\[
\begin{align*}
\text{calc.} & = -(144.6 \pm 3.3), I \\
\text{exp.} & = -(159.8 \pm 4.5) \text{ kJ·mol}^{-1}, R^2 = 0.999, \text{RMS} = 2.7 \text{ kJ·mol}^{-1}
\end{align*}
\]

### 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. | ΔH | Calc. | Lit. | ΔH | Calc. | Lit. | ΔH | Calc. | Lit. | ΔH | Calc. | Lit. | ΔH | Calc. | Lit. | ΔH | Calc. | Lit. | ΔH | Calc. | Lit. | ΔH | Calc. | Lit. | ΔH | Calc. | Lit. | ΔH | Calc. | Lit. | ΔH |
|----------|------|----|------|-----|----|------|-----|----|------|-----|----|------|-----|----|------|-----|----|------|-----|----|------|-----|----|------|-----|----|------|-----|----|------|-----|----|------|-----|----|
| 123.6    | 134  | [68]|      |     |    |      |     |    |      |     |    |      |     |    |      |     |    |      |     |    |      |     |    |      |     |    |      |     |    |      |     |    |      |     |    |      |     |    |
| 150.4    | 168  | [69]|      |     |    |      |     |    |      |     |    |      |     |    |      |     |    |      |     |    |      |     |    |      |     |    |      |     |    |      |     |    |      |     |    |      |     |    |
| 162.3    | 178  | [70]|      |     |    |      |     |    |      |     |    |      |     |    |      |     |    |      |     |    |      |     |    |      |     |    |      |     |    |      |     |    |      |     |    |      |     |    |
| 28.4     | 34   | [71]|      |     |    |      |     |    |      |     |    |      |     |    |      |     |    |      |     |    |      |     |    |      |     |    |      |     |    |      |     |    |      |     |    |      |     |    |
| 47.7     | 58   | [71]|      |     |    |      |     |    |      |     |    |      |     |    |      |     |    |      |     |    |      |     |    |      |     |    |      |     |    |      |     |    |      |     |    |      |     |    |
| 19.1     | 25   | [71]|      |     |    |      |     |    |      |     |    |      |     |    |      |     |    |      |     |    |      |     |    |      |     |    |      |     |    |      |     |    |      |     |    |      |     |    |
| Electronegativity [72] |      |      |    | --- | 4.0 |    | 3.0 |    | 2.8 |    | 2.5 |    |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |
| Ionization energy (kJ·mol^-1) [73] |      |      |    | --- | 1681 |    | 1251 |    | 1140 |    | 1008 |    |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |
From Lit.: F = (7.5 ± 5.0), Cl = -(126.8 ± 4.3), Br
= -(156.8 ± 6.1), I
= -(174.0 ± 8.2) kJ·mol⁻¹, R²
= 0.998, RMS = 5.0 kJ·mol⁻¹ (3)

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

From ΔG : F = 0.0, Cl = -(121.0 ± 2.4), Br
= -(149.0 ± 2.4), I
= -(166.4 ± 2.4) kJ·mol⁻¹, R²
= 0.999, RMS = 3.4 kJ·mol⁻¹ (4)

From Lit.: F = 0.0, Cl = -(130.5 ± 4.2), Br
= -(164.2 ± 4.2), I
= -(185.2 ± 4.2) kJ·mol⁻¹, R²
= 0.999, RMS = 5.9 kJ·mol⁻¹ (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:

From ΔG : F = 0.0, Cl = -(123.0 ± 0.6), Br
= -(151.0 ± 0.6), I
= -(170.4 ± 0.7), interaction F/I
= -(8.1 ± 1.0) kJ·mol⁻¹, R² = 1.000, RMS
= 0.7 kJ·mol⁻¹ (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 (kJ·mol⁻¹). With this last one we obtain:

From ΔG : Halogen values of eq.6
+ (0.982 ± 0.003) ionization energies, n
= 4, R² = 1.000, RMS = 0.7 kJ·mol⁻¹ (7)

From Lit.: Halogen values of eq.6
+ (1.081 ± 0.003) ionization energies, n
= 4, R² = 1.000, RMS = 1.6 kJ·mol⁻¹ (8)

The very good quality of Eqs. (7) and (8) proves that our analysis of the energetic values of the six SN₂ 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.

Acknowledgements This work was carried out with financial support from the Ministerio de Ciencia, Innovación y Universidades (PGC2018-094644-B-C22) and Comunidad Autónoma de Madrid (P2018/EMT-4329 AIRTEC-CM). Thanks are also given to the CTI (CSIC) for their continued computational support.

Availability of data and material The data that support this research are available in the article.

Code availability Not applicable.

Author contribution LA 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.

Funding Open Access funding provided thanks to the CRUE-CSIC agreement with Springer Nature. Ministerio de Ciencia, Innovación y Universidades (PGC2018-094644-B-C22), and Comunidad Autónoma de Madrid (P2018/EMT-4329 AIRTEC-CM)

Declarations

Conflict of interest The authors declare no competing interests.

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