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Global Electrophilicity Study of the Reaction of Pyrroles with *N*-Halo Compounds and the Rate-Determining Step

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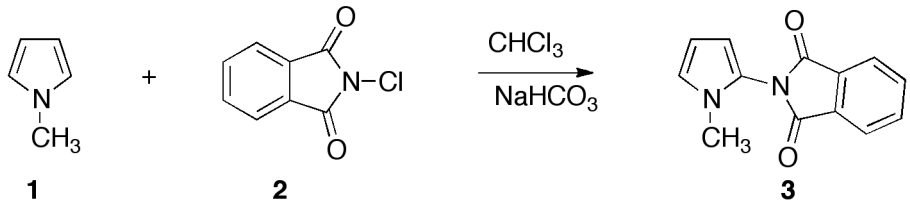
Abstract

Pyrroles (nucleophiles) can react with *N*-halo compounds (electrophiles) to give either addition-elimination or halogenation products. Global electrophilicity (ω) has been used to study electrophile-nucleophile combinations. The ω values of the *N*-halo compounds (n = 22) used were calculated using DFT/B3LYP. No correlation was observed between ω and the pathway of reaction/non-reaction. A single parameter (ω) could not explain the results of the competing reactions that are taking place in this system–reactions that appear to depend on the *N*-halogen (Cl, Br, I) nucleophilicity/basicity and possibly hardness of the leaving group. These calculations confirmed that the rate-determining step of the addition-elimination process was not the formation of an σ-complex, but its subsequent reaction. Calculations suggested that deprotonation of the σ-complex was the rate-determining step in the halogenation reactions. It was also possible to examine the effects of the structure of the *N*-halo-compound and the halogen.

Keywords: global electrophilicity scale, pyrroles, *N*-halo compounds, addition-elimination, halogenation

1. Introduction

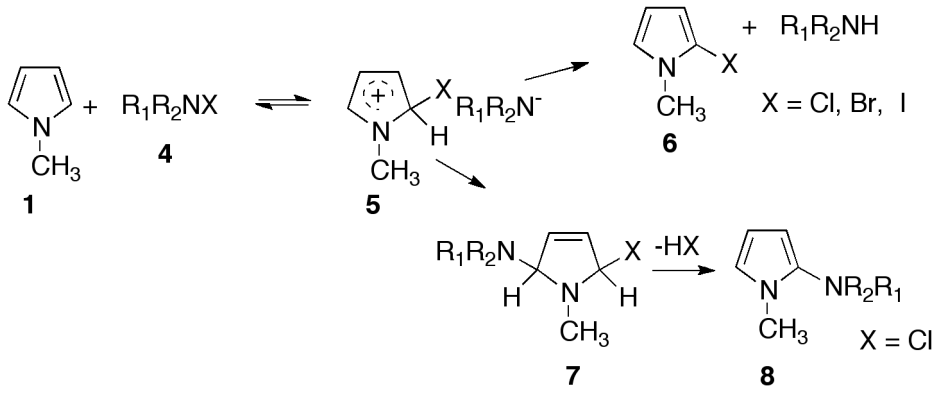
Pyrroles can undergo electrophilic aromatic substitution by a process of addition-elimination (σ-substitution) (De Rosa & Brillembourg, 1986). Reaction of a 1-substituted pyrrole with an *N*-halo derivative gave a product in which a nitrogen moiety became attached to C2 of the pyrrole ring. Studies have been carried out to determine the generality of this reaction. It was found that the halogen (De Rosa & Cabrera-Nieto, 1988; De Rosa & Marwaha, 1994) and the structure of the *N*-halo compound (De Rosa, Cabrera-Nieto, & Ferrer-Gago, 1989) determined which process was observed: addition-elimination or halogenation. In some cases no reaction was observed, in the presence of base (De Rosa et al., 1989). Scheme 1 is an example of a typical addition-elimination reaction:



1 **2** **3**

Scheme 1. Electrophilic substitution by addition-elimination

It was proposed that the reaction of a 1-substituted pyrrole with an *N*-halo compound led to the initial formation of an ion-pair (De Rosa & Brillembourg, 1986; De Rosa & Cabrera-Nieto, 1988). Collapse of the ion-pair, followed by elimination of HX, gave the addition-elimination product **8** whereas, deprotonation of the σ-complex **5** led to halogenation (Scheme 2).



Scheme 2. Possible mechanistic pathways

The reaction under study is between an electrophilic *N*-halo compound and a nucleophilic pyrrole resulting in the formation of an ion-pair. Mechanisms of electrophile-nucleophile combinations have been studied using the global electrophilicty index (ω) (Parr, Szentpaly, & Liu, 1999). Recently it has been used to study polar Diels-Alder reactions (Domingo & Saez 2009), the reactions of superelectrophiles with aromatic and heteroaromatic compounds (Lakhdar et al., 2010), and the reaction of benzhydryl cations (Chamorro, Duque-Norena, & Perez, 2009a, 2009b)–systems that involve electrophile-nucleophile combinations (Terrier, Dust, & Buncel, 2012). In order to gain a greater insight into the possible mechanisms of the reactions of 1-substituted pyrroles with an *N*-halo compound the ω values of the *N*-halo compounds used were calculated. It could then be possible to use the ω values of the *N*-halo compounds to predict if addition-elimination, halogenation, or no reaction would take place with a given *N*-halo compound.

2. Computational Methods

The global electrophilicity index (ω) of the *N*-halo compounds and pyrroles were calculated following the same approaches as reported by Domingo (Domingo, Saez, & Perez, 2007; Domingo et al., 2009). The values depend on two properties, the electronic chemical potential μ, and the chemical hardness η.

$$\omega = \frac{\mu^2}{\eta} \tag{1}$$

The electronic chemical potential μ and the chemical hardness η were calculated in terms of the one-electron energies of the frontier molecular orbital HOMO (ε_H) and LUMO (ε_L), at the ground state (Parr & Pearson, 1983). The electronic chemical potential μ is associated with the charge transfer ability of the molecule in its ground state and calculated by:

$$\mu \approx \frac{\varepsilon_H + \varepsilon_L}{2} \tag{2}$$

The chemical hardness η is associated with the resistance of the molecule to exchange electronic charge with the environment in its ground state and calculated by:

$$\eta \approx \varepsilon_L - \varepsilon_H \tag{3}$$

We used the density functional theory methodology, DFT/B3LYP, with 6-31G* basis set using the Gaussian 09 program (Frisch et al., 2004) to determine the optimized geometry of the ground state. In Table 1 the global electrophilicity index (ω), electronic potential (μ) and chemical hardness (η) are reported based on DFT/B3LYP methodologies with 6-31G* basis set. Since the 6-31G* basis set does not include iodine, we also calculated values for all molecules with 3-21G* basis set, which contains iodine, in DFT/B3LYP methodology. For the *N*-chloro-*N*-(4-X-phenyl)-benzenesulfonamides the electrophilicity values for the most stable conformations were used. The effect of *N*-chlorination on the conformational preferences of *N*-(4-X-phenyl)-benzenesulfonamides will be the subject of a separate study.

We determined the electrophilicity values based on three different methodologies DFT/B3LYP, HF and MP2 methodologies. In the DFT/B3LYP methodologies we report the values with two different basis sets, 6-31G* and 3-21G* and in the HF and MP2 methodologies we report the values only with the basis set 6-31G*. All three

methodologies show similar trends in the ω values. See suplementary information for comparisons. In Table 2 we report the global electrophilicity values based on the three methodologies in 6-31G* basis set and also included are the 3-21G* basis set values for DFT/B3LYP methodology.

Table 1. The global electrophilicity index (ω), electronic potential (μ) and chemical hardness (η) values (eV) based on DFT/B3LYP methodologies with 6-31G* basis set

#	Compound	Reaction[7]	μ	η	ω
1	*N*-Chloroacetanilide[1]	AE	-4.032	4.792	1.70
2	*N*-Chlorosuccinimide[2]	AE	-4.385	6.248	1.54
3	*N*-Bromosuccinimide[2]	H	-4.654	5.528	1.96
4	*N*-Iodosuccinimide[2]	H	-	-	-
5	*N*-Chlorophthalimide[2]	AE	-4.958	4.806	2.56
6	*N*-Bromophthalimide[2]	H	-4.837	4.699	2.49
7	*N*-Iodophthalimide[2]	H	-	-	-
8	*N*-Chlorobenzotriazole[3]	H	-4.161	5.152	1.68
9	*N*-Chloromaleimide[3]	AE	-5.355	4.568	3.14
10	*N*-Chlorobenzimidazole[3]	H	-3.911	4.798	1.59
11	*N*-Chlorobenzamide[3]	NR	-4.221	5.760	1.55
12	*N*-Chloroacetamide[3]	NR	-4.272	5.734	1.59
13	*N*-Chlorourea[3]	NR	-4.288	5.719	1.61
14	*N*-Chloro-*N*,*N*'-dimethylurea[3]	NR	-3.999	5.421	1.47
15	*N*-Chloro-*N*-(phenyl)-benzenesulfonamide[4,6]	AE	-4.142	5.043	1.70
16	*N*-Chloro-*N*-(4-methoxyphenyl)-benzenesulfonamide[4,6]	AE	-3.855	4.609	1.61
17	*N*-Chloro-*N*-(4-methylphenyl)-benzenesulfonamide[4,6]	AE	-4.039	4.918	1.66
18	*N*-Chloro-*N*-(4-fluorophenyl)-benzenesulfonamide[4,6]	AE	-4.201	4.957	1.78
19	*N*-Chloro-*N*-(4-nitrophenyl)-benzenesulfonamide[4,6]	AE	-4.955	4.423	2.78
20	1,3-Dichloro-5,5-dimethylhydantoin[5]	AE	-4.634	5.382	2.00
21	1,3-Dichloro-5-methyl-5-phenylhydantoin[5]	AE	-4.530	5.068	2.02
22	1,3-Dichloro-5,5-diphenyllhydantoin[5]	AE	-4.426	5.001	1.96
23	1-Methylpyrrole		-2.072	6.699	0.32
24	1-Ethylpyrrole		-2.046	6.706	0.31
25	1-tert-butypyrrole		-1.945	6.737	0.28
26	1-Phenylpyrrole		-2.999	5.308	0.85

[1] (De Rosa & Brillembourg, 1986).

[2] (De Rosa & Cabrera-Nieto, 1988).

[3] (De Rosa et al., 1989).

[4] (De Rosa et al., 1991).

[5] (De Rosa, Melenski, & Holder, 1993b).

[6] The value is based on the minimum energy conformer.

[7] AE = addition-elimination reaction; H = halogenation; NR = no reaction.

Table 2. The global electrophilicity values (eV) based on DFT/B3LYP, HF and MP2 methodologies

#	Compound	DFT/B3LYP 6-31G*	DFT/B3LYP 3-21G*	HF 6-31G*	MP2 6-31G*
1	*N*-Chloroacetanilide[1]	1.70	1.64	0.39	0.36
2	*N*-Chlorosuccinimide[2]	1.54	1.45	0.45	0.51
3	*N*-Bromosuccinimide[2]	1.96	1.68	0.58	0.64
4	*N*-Iodosuccinimide[2]	(2.30)[7]	2.25	-	-
5	*N*-Chlorophthalimide[2]	2.56	2.56	0.84	0.93
6	*N*-Bromophthalimide[2]	2.49	2.45	0.81	0.90
7	*N*-Iodophthalimide[2]	(2.46)[7]	2.42	-	-
8	*N*-Chlorobenzotriazole[3]	1.68	1.78	0.47	0.54
9	*N*-Chloromaleimide[3]	3.14	3.15	1.03	1.15
10	*N*-Chlorobenzimidazole[3]	1.59	1.60	0.30	0.31
11	*N*-Chlorobenzamide[3]	1.55	1.44	0.50	0.53
12	*N*-Chloroacetamide[3]	1.59	1.41	0.44	0.51
13	*N*-Chlorourea[3]	1.61	1.34	0.46	0.53
14	*N*-Chloro-*N*,*N*'-dimethylurea[3]	1.47	1.26	0.37	0.45
15	*N*-Chloro-*N*-(phenyl)-benzenesulfonamide[4,6]	1.70	1.69	0.49	0.53
16	*N*-Chloro-*N*-(4-methoxyphenyl)-benzenesulfonamide[4,6]	1.61	1.59	0.41	0.46
17	*N*-Chloro-*N*-(4-methylphenyl)-benzenesulfonamide[4,6]	1.66	1.64	0.46	0.49
18	*N*-Chloro-*N*-(4-fluorophenyl)-benzenesulfonamide[4,6]	1.78	1.78	0.52	0.57
19	*N*-Chloro-*N*-(4-nitrophenyl)-benzenesulfonamide[4,6]	2.78	2.80	0.88	0.99
20	1,3-Dichloro-5,5-dimethylhydantoin[5]	2.00	1.89	0.53	0.62
21	1,3-Dichloro-5-methyl-5-phenylhydantoin[5]	2.02	1.98	0.43	0.46
22	1,3-Dichloro-5,5-diphenyllhydantoin[5]	1.96	1.94	0.42	0.45
23	1-Methylpyrrole	0.32	0.31	0.05	0.06
24	1-Ethylpyrrole	0.31	0.30	0.05	0.06
25	1-tert-butypyrrole	0.28	0.28	0.04	0.05
26	1-Phenylpyrrole	0.85	0.86	0.21	0.21

[1] (De Rosa & Brillembourg, 1986).

[2] (De Rosa & Cabrera Nieto, 1988).

[3] (De Rosa et al., 1989a). [4.](De Rosa et al., 1991).

[5] (De Rosa, Melenski & Holder, 1993b).

[6] The value is based on the minimum energy conformer.

[7] The values in parenthesis are the theoretically calculated values based on the comparison to 3-21G* basis set of DFT/B3LYP.

3. Results and Discussion

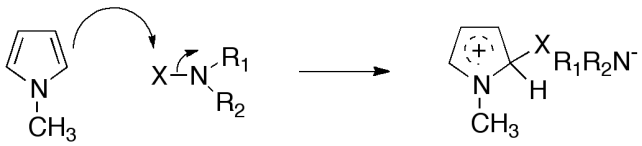
Unless specified differently, the electrophilicity values (in units of eV) determined by DFT/B3LYP methodology with 6-31G* basis set will be used below.

3.1 Effect of ω

Electrophilicity index (ω) values (B3LYP) of 1.54-3.14 were calculated for *N*-halo compounds that gave addition-elimination products (n = 12), 1.59-2.49 for halogenation (n = 6), and 1.47-1.61 for unreactive compounds (n = 4). No correlation was observed between the value of ω and the pathway of reaction/non-reaction. This can be clearly seen by comparing the very similar ω values of *N*-chlorosuccinimide

(1.54), *N*-Chlorobenzimidazole (1.59) and *N*-chlorobenzamide (1.55) that resulted in addition-elimination, chlorination, and no reaction respectively. Based on the data in Tables 1 and 2 it is not possible to predict the mode of reaction from the value of ω for reasons that will be discussed below.

The data did allow us to examine several other interesting aspects of this reaction. Ion-pair formation can be seen to be a halogenophilic reaction–nucleophilic attack on a halogen with an anionic nitrogen-leaving group (Scheme 3) and thus should depend on both the halogen and the leaving group (Zefirov & Makhon'kov, 1982). Data in Tables 1 and 2 allowed us to examine both of these effects.



1 **4** **5**

Scheme 3. Nucleophilic attack by 1-methylpyrrole on halogen

3.2 Halogen Effect

The halogen effect can be observed in the series of *N*-halo succinimides and phthalimides where reactions with chloro, bromo and iodo derivatives have been studied (De Rosa & Cabrera Nieto, 1988). The general order for halogenophilic reactions (where the halogen is bonded to carbon and the nucleophile is an anion) is I>Br>>Cl (Zefirov et al., 1982; Bunnett, 1972). Examples of halogenophilic reactions of *N*-chloro and *N*-bromo derivatives have been reported (Lee, Terrazas, Pippel, & Beak, 2003; Scharf, 1974) but, to our best knowledge, no general trend for the effect of the halogen has been reported in reactions of *N*-halo derivatives with either charged or uncharged nucleophiles. Interestingly in this study ω values are I>Br>Cl for *N*-halosuccinimides, but the opposite trend is observed for *N*-halophthalimides (B3LYP/3-21G* ω values were used). It has been reported that the order of halogenophilic reactivity of halogens is not the same for all reactions, and can also depend on the nucleophile (Zefirov et al., 1982).

Reaction of a series of *N*-haloimides with 1-methylpyrrole (**1**) gave a set of ion-pairs **5** in which the only difference in structure is the nature of X (Cl, Br or I). Therefore any difference in reaction mode can be attributed to the halogen. Observation of an isotope effect has shown that the slow step of the addition-elimination reaction is not the formation of the ion-pair, but its subsequent reaction (De Rosa, Shadle & Foster, 1993a). This has been attributed to the effect of the halogen on the aromatic character of pyrrole. The presence of a chloro group decreases the aromaticity (Kao, Hinde, & Radom, 1979) of the pyrrole ring and makes addition-elimination more likely. An isotope effect has also been observed in the acid-catalyzed chlorination of 1-methylpyrrole with *N*-chlorobenzamides; the second step, loss of a proton, is rate-determining (De Rosa & Marquez, 1989). It is possible that in the present study, where halogenation occurred under neutral conditions, the rate-determining step was also the loss of a proton. There is as yet no direct experimental evidence for this possibility.

Several studies have appeared in which correlations of reactivity with respect to ω were inconclusive (Nalbantova, Cheshmedzhieva, Hadjieva, Ilieva, & Galabov 2011; Steglenko et al., 2011). In one it was because the reaction of the electrophile with the nucleophile was not the rate-determining step (Nalbantova et al., 2011). Recently it was reported (Lakhdar & Mayr, 2011) that it was possible to carry out a correlation with respect to electrophilicity using the Mayr scale (Mayr & Patz, 1994) when a catalyst was added to make the electrophile-nucleophile combination step rate determining.

3.3 Leaving Group Effect

Previously we had proposed that the reactivity of the *N*-chloro compounds was determined by the pK_a (as a measure of leaving group ability (nucleofugality) of the nitrogen anion) of the parent nitrogen compound (De Rosa et al., 1989). When a poor leaving group was present, no reaction would be expected. In this study no correlation was found between pK_a and ω of the *N*-halo compounds used. For the reaction of 1-methylpyrrole (**1**) with *N*-chloro-compounds, the ion-pair **5** obtained differed only in the nature of the counter ion ($R_1R_2N^-$) present. This implies that some other property or properties of the leaving group, rather than just ω, is responsible for the reaction pathway observed in a particular case. Reactions in which there was delocalization of the negative charge on the nitrogen of the chlorine carrier, led to either addition-elimination or chlorination. This can be seen

be comparing the results with *N*-chloroacetanilide (ω = 1.64) and *N*-chlorobenzamide (ω = 1.44). The former, where delocalization of the negative charge into the benzene ring was possible, reacted by addition-elimination, whereas the latter, where delocalization into the ring was not expected to be important, did not react. For those cases where reaction did take, the dichotomy between addition-elimination and chlorination could be a function of the interplay between the nucleophilicity (addition-elimination) and basicity (chlorination) of the leaving group.

While the ω values of the *N*-chloro derivatives of benzamide, acetamide, urea, and *N*,*N*'-dimethylurea were low (1.26–1.44), they overlapped the lower range of *N*-halo compounds that gave addition-elimination products (see Tables 1 and 2). This suggested the possibility that ion-pair **5** could have formed, but its collapse to starting materials was faster than either of the pathways leading to addition-elimination or halogenation. Based on their structures, the counter ions obtained in these cases would be expected to bear more of the negative charge on nitrogen. Interestingly this suggested the possibility that the hardness (Pearson, 1963) of the anionic counter ion in **5** may also be playing a role in determining the mechanistic pathway(s). The solvent could also be playing a role. Previous experimental results indicated that solvents of low to medium polarity favored addition-elimination (De Rosa & Cabrera-Nieto, 1988). It was suggested that this was because tight ion-pairs favored addition-elimination. This could also favor collapse to starting materials.

4. Conclusions

Once the ion-pair is formed it can lead to halogenation by loss of a proton, collapse to give the addition-elimination product with the elimination of HX, or revert to starting materials. This study indicated that a single parameter (ω) could not be used to explain the results of the competing reactions that are taking place in this system–reactions that appear to depend on the *N*-halogen, nucleophilicity/basicity and possibly hardness of the leaving group, and given that ω values are calculated in the gas phase–the solvent. Global electrophilicity can be used to predict electrophile-nucleophile combinations, but not necessarily what happens after the initial step, particularly if it is not rate determining. The results of this study supported previous reports (De Rosa & Brillembourg, 1986; De Rosa et al., 1993a) that the reaction of the initially formed σ-complex was the rate-determining step in the addition-elimination reaction, and suggested similar results for halogenation (Scheme 2).

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