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Predicting Regioselectivity in Nucleophilic Aromatic Substitution

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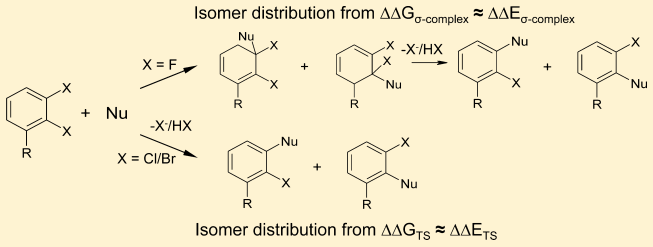
Supporting Information

ABSTRACT: We have investigated practical and computationally efficient methods for the quantitative prediction of regioisomer distribution in kinetically controlled nucleophilic aromatic substitution reactions. One of the methods is based on calculating the relative stabilities of the isomeric σ-complex intermediates using DFT. We show that predictions from this method can be used quantitatively both for anionic nucleophiles with F^- as leaving group, as well as for neutral nucleophiles with HF as leaving group. The σ-complex approach failed when the leaving group was Cl/HCl or Br/HBr, both for anionic and neutral nucleophiles, because of difficulties in finding relevant σ-complex structures. An approach where we assumed a concerted substitution step and used such transition state structures gave quantitatively useful results. Our results are consistent with other theoretical works, where a stable σ-complex has been identified in some cases, whereas others have been indicated to proceed via a concerted substitution step.



INTRODUCTION

Nucleophilic aromatic substitution is a synthetically and industrially important reaction type, and it can proceed via a number of different reaction mechanisms, e.g., S_N1,[1] elimination−addition,[2] and metal-catalyzed substitution.[3−5] By far, the most important mechanism for nucleophilic aromatic substitution[1] is however the two-step addition−elimination mechanism, commonly known as S_NAr. Here, the active nucleophile is added to a substituted aromatic carbon atom, followed by departure of the leaving group. The intermediate containing both the nucleophile and the leaving group is known as a Meisenheimer complex or σ-complex.[6,7]

Prediction of positional selectivity in a S_NAr reaction step can be a key part of the evaluation of theoretical synthetic route alternatives to a target molecule, and in this evaluation, computational chemistry is a powerful tool. There are many different computational methods where the different positions in the starting structure is given some sort of reactivity index.[8−13] Many of these methods are quite successful in making qualitatively correct predictions of the selectivity pattern in S_NAr reactions, but quantitative predictions are difficult since the structure and solvation of the transition state is not taken into account. A more laborious approach, but one which should enable quantitative predictions of the selectivity pattern in S_NAr reactions, is to calculate the potential energy surface in each case, and such work has been done recently within the DFT framework.[14,15]

In two recent papers, we have described a method for predicting product isomer ratios based on calculating the relative stability of the isomeric σ-complex intermediates using DFT. The first paper deals with S_EAr reactions,[16] and in the second, we applied this method to S_NAr reactions with anionic nucleophiles and F^- as leaving group.[17] An advantage with this approach is that it replaces a calculation of a potential energy surface, including two transition state structures, with an optimization to a local minimum, while preserving an accuracy that in many cases is sufficient for the quantitative prediction of regioisomeric outcome. The purpose of the work presented in this paper is to evaluate if and how this method can be extended to incorporate a larger space of nucleophiles/nucleofuges (incoming/leaving groups). More specifically we have, beside anionic nucleophiles, also investigated neutral nucleophiles, like amines, and also, beside F^-, the leaving groups Cl^- and Br^-. We report when our previous approach (the "σ-complex approach") can be successfully applied, but also when it cannot be applied, and then we use a transition state approach instead (the "TS approach").

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A necessary, but not sufficient, condition for the applicability of our σ-complex approach is the possibility of finding a reaction intermediate that represents a true minimum on the potential energy surface. The nature of the Meisenheimer adduct in a S_NAr reaction has been investigated by quantum chemical calculation methods both by Glukhovtsev et al.[15] and more recently by Fernández et al.[18] Both groups came to the conclusion that it is a stable σ-complex in some cases and a transition state structure in others. For the scope of our investigation, it is important to consider their results; if the leaving group is bound to the ring via an element in the second row of the periodic table (i.e., −F, $-NH_2$, −OH), there exists a stable σ-complex, and the substitution step in the reaction thus proceeds through the putative stepwise addition/elimination mechanism.[18] When the leaving group is bound via an element in the third or fourth row, like Cl and Br, the reaction is usually concerted, and a stable σ-complex can only be found if the substrate is highly stabilized, e.g., by several nitro substituents.[18] Consequently, with leaving groups like Cl and Br, our previously used σ-complex approach[16,17] is not likely to succeed.

METHODS

The σ-complex approach involves the following assumptions: first, that the reaction is kinetically controlled; second, that the energy differences between the isomeric transition states of the rate determining step can be approximated with the energy differences between the corresponding intermediate σ-complexes, in accordance with the Hammond postulate; and third, that the entropy terms ($T\Delta S$) for the reactions forming the different regioisomers will be very similar, and these terms therefore will cancel out ($\Delta\Delta E \cong \Delta\Delta G$). The TS approach involves the same first and third assumptions as above, but obviously not the second one.

Calculations were carried out on all possible σ-complexes or TS structures; first, the geometry of each σ-complex or TS structure, without coordinated catalysts, promoters or counterions is optimized in vacuo or directly in solution through the continuum solvation models available in the softwares, using the DFT functional B3LYP with the 6-31+G(d,p) basis set (unless otherwise noted). We used both the Jaguar[19] and the Gaussian[20] suite of programs. Second, if the structure is calculated in vacuo, the solvation free energy is taken into account by an a posteriori energy correction from single point calculations using the previously optimized structures and the continuum solvation models within the same softwares.[19,20] In the Jaguar program, we used the Poisson−Boltzmann finite element solvation model (PBF) and in Gaussian the integral equation formalism variant of PCM (IEFPCM). The exact procedure in each case is given in footnotes to the respective result tables in the Results section (Tables 1−4). Frequency calculations were carried out for all the TS species to establish their nature as transition states. Third, the distribution of isomers is calculated from the Boltzmann distribution of the σ-complexes or TS structures, at the temperature used experimentally in each specific reaction.

Different conformations of the σ-complexes or TS structures were considered in this study only if we judged this to be necessary (on the basis of their chemical structure). However, no systematic conformational searches were performed, and when different conformers were calculated, we did not use any Boltzmann summations, but the conformer with the lowest energy was used.

RESULTS

We have chosen to divide the results section into the following parts: (i) anionic nucleophiles with F^- as leaving group, (ii) neutral nucleophiles with HF as leaving group, (iii) anionic nucleophiles with Cl^- or Br^- as leaving group, and (iv) neutral nucleophiles with HCl or HBr as leaving group. The performance of our regioselectivity index candidates was examined on the basis of correlations with experimentally found regioisomer distributions of representative S_NAr reactions. The molecular systems used in our investigation are all taken from the literature, and the labeling of the positions is shown in the figures belonging to each result part. The detailed results are presented in separate tables, one for each result part, with the lowest energy structure in each case taken as zero. The calculated values are given both as an energy difference, in kcal/mol, and in parentheses, as the corresponding regioisomeric ratio (%). The calculated isomer distributions have been adjusted for degenerate positions. The experimental isomer distributions are also given both as regioisomeric ratio, in parentheses (%), as well as a calculated energy difference in kcal/mol. The experimental regioisomer ratios have been determined in different ways, e.g., isolated yields and ^{19}F NMR; see the references to the original papers, given in the footnotes to each result table, for the exact procedure in each case. The corresponding energy differences have been calculated by us.

Anionic Nucleophiles and F^- As Leaving Group. The molecules used for this case are shown schematically in Figure 1. Relative energies and regioisomer ratios for all σ-complexes

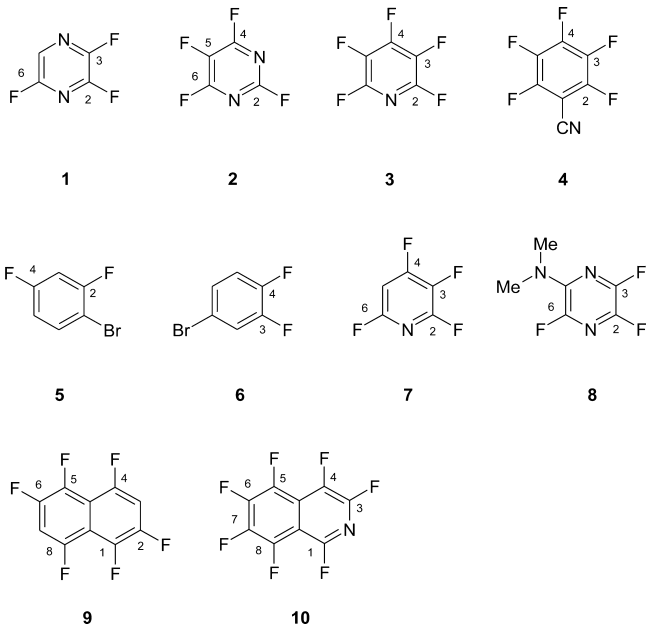

Figure 1. Schematic diagram of the structures studied in Table 1, also showing the labeling of positions.

with an energy within 4.0 kcal/mol of the lowest one are shown in Table 1. This case has been dealt with by us in a previous paper,[17] but we include it here for the sake of completeness.

Predictions are based on the σ-complex approach, and the agreement with experimental data is very good; the method can be used for quantitative predictions. The solvation calculation used in the method gives an improvement of the prediction; the average absolute deviation goes from 1.0 kcal/mol in vacuo to 0.6 kcal/mol in solvent.[21] It is worth noticing that the proposed method is able to correctly reproduce the experimental observation that the regioisomeric outcome changes from predominantly position 1 to position 6 when the nucleophile is changed from methoxide to hydrosulfide in reactions with hepta-fluoroisoquinoline (**10** in Figure 1) as the substrate (Table 1, entries 10 and 11). The absolute deviation between

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Table 1. Modeling of Anionic S_NAr, F as Leaving Group[a]

entry	isomer	in vacuo σ-complex[b]	solvent σ-complex[c]	experimental
1	Reaction of (**1**) with the anion of methanol[d,m]			
	2	0.0 (100)	0.0 (100)	(100)
2	Reaction of (**2**) with azide[e,m]			
	4	0.0 (100)	0.0 (100)	(100)
3	Reaction of (**3**) with the anion of methanol[f,m]			
	4	0.0 (100)	0.0 (100)	(100)
4	Reaction of (**4**) with azide[g,m]			
	4	0.0 (98)	0.0 (96)	(100)
	2	3.3 (2.5)	2.8 (4.5)	(0)
5	Reaction of (**5**) with the anion of benzyl alcohol[h]			
	2	0.0 (89)	0.0 (95)	0.0 (95)
	4	1.2 (11)	1.7 (5)	1.7 (5)
6	Reaction of (**6**) with the anion of benzyl alcohol[h]			
	3	0.0 (95)	0.0 (96)	0.0 (91)
	4	1.7 (5)	1.8 (4)	1.3 (9)
7	Reaction of (**7**) with the anion of methanol[f,m]			
	4	0.0 (98)	0.0 (96)	0.0 (95)
	2	2.5 (1.5)	1.8 (4)	1.8 (5)
8	Reaction of (**8**) with the anion of methanol[d,m]			
	6	0.0 (37)	0.0 (58)	0.0 (90)
	2	−0.3 (63)	0.2 (42)	1.3 (10)
9	Reaction of (**9**) with the anion of methanol[i]			
	2	0.0 (75)	0.0 (88)	0.0 (70)
	4	1.9 (3)	1.7 (5)	0.7 (20)
	1	0.7 (22)	1.5 (7)	1.1 (10)
10	Reaction of (**10**) with the anion of methanol[j,m,n]			
	1	0.0 (83)	0.0 (99)	0.0 (93)
	6	0.6 (17)	1.7 (1)	1.0 (7)
	8	3.1 (0)	4.3 (0)	(0)
11	Reaction of (**10**) with the hydrogen sulfide anion[k,m,n]			
	1	4.2 (0)	1.7 (4)	1.3 (8)
	6	0.0 (100)	0.0 (96)	0.0 (92)
	8	4.1 (0)	3.6 (0.1)	(0)
12	Reaction of (**10**) with the anion of methanethiol[l,m,n]			
	1	4.2 (0)	3.1 (0.0)	0.3 (30)
	6	0.0 (100)	0.0 (100)	0.0 (70)

[a]All data are from ref 17. Relative energies are given in kcal/mol; isomer distributions are given in %, in parentheses. The compound numbers in bold refer to Figure 1. The calculated isomer distributions have been adjusted for degenerate positions. Experimental relative activation energies were deduced from the product distribution. [b]Structures found by optimization in vacuo using the 6-31G(d,p) basis.[19] [c]A posteriori single point with the PBF solvent model.[19] [d]Sodium methoxide in methanol at rt.[22] [e]NaN_3 in acetonitrile at 0 °C.[23] [f]Sodium methoxide in methanol at rt.[24] [g]NaN_3 in acetone/water at reflux.[25] [h]Benzyl alcohol with excess NaH in THF at rt overnight.[26] [i]Sodium methoxide in methanol at rt.[27] [j]Sodium methoxide in methanol at −82 to −84 °C.[28] [k]Sodium hydrosulfide (NaHS) in DMF and ethylene glycol at −5 to 2 °C.[28] [l]Sodium methanethiolate in ethanol at −85 to −90 °C.[28] [m]No other isomers were reported experimentally. The isomers not included in this table had computed energies >4.0 kcal/mol or unreasonable structures. [n]The solvent calculation was performed without diffuse functions because of technical convergence problems.

the solvent calculation and experiment is larger than 1 kcal/mol for two of the entries (Table 1, entry 8 and 12), but the deviation between the corresponding in vacuo calculations and experiment is larger still. It is likely that one would have to include explicit solvent molecules in the calculations in order to further improve the prediction for these two entries.

Neutral Nucleophiles and HF as Leaving Group. Reactions with neutral nucleophiles, like amines, constitutes a special case of S_NAr reactions, and they have attracted great mechanistic interest in recent years.[29−33] Here, the generally accepted first step for a reaction occurring in highly polar media (water, ACN, DMSO) leads to the formation of a zwitterionic σ-complex. The decomposition step is a bit more involved compared to the case of anionic nucleophiles, since the system formally loses a proton in addition to F^-. A number of competitive decomposition processes have been postulated; expulsion of F^- followed by deprotonation,[29] base-catalyzed deprotonation followed by loss of F^-,[29,34] and the expulsion of HF in a concerted manner.[35] Which step in the reaction mechanism that is rate-determining is largly dependent upon the solvent.[29,30] There are many examples where the decomposition step is rate-determining; this is the case for the specific base/general acid (SB-GA) mechanism in dipolar aprotic solvents.[36,37] Furthermore, it has been shown that in apolar solvents like THF, the nature of the intermediate can be different (anionic instead of zwitterionic) and that the first step is under general base catalysis, while the elimination step is general-acid-catalyzed.[34]

Our first attempt with neutral nucleophiles was to proceed in the same way as for anionic nucleophiles.[17] However, no stable zwitterionic σ-complexes were found in vacuo or by geometry optimizations in nonpolar solvents, even when larger basis sets were used. Other authors have experienced similar difficulties.[36,38−40] Some studies indicate that these reactions may proceed via a concerted path without σ-complex, at least in nonpolar media. However, the difficulties in finding zwitterionic structures in vacuo is not very surprising, considering that the energy for separating the charges is high without the stabilizing effect of the solvent. Geometry optimizations in polar solvents gave stable zwitterionic σ-complexes in most cases.

We have also calculated the TS of the decomposition step, where we have chosen TS structures where H and F leave in a concerted manner, as a model for all reactions in Table 2. These structures were optimized in vacuo. In order to investigate the possibility/likelihood that these reactions proceed via an anionic intermediate[34] (even though the experimental conditions suggest a neutral nucleophile), comparisons were also made using calculations with the corresponding anionic σ-complex (attack with the anion of the amine).

The studied molecules are shown schematically in Figure 2 and also in Figure 1. Relative energies and regioisomer ratios of all σ-complexes, TS-structures, and anionic σ-complexes for the investigated systems are listed in Table 2. We have also calculated the relative energies of some of the final products in order to investigate kinetic versus thermodynamic control. They do not correlate at all with the experimentally found regioisomer distributions, which support our assumption of kinetic control.

Predictions from both the solvent-corrected σ-complex approach and the solvent-corrected TS approach give equally good results and can be used quantitatively; the average absolute deviation was 0.5 and 0.6 kcal/mol, respectively. The approach with anionic amine nucleophiles (even though the experimental conditions indicate neutral amines) shows a deterioration of the results with the addition of the solvation correction. It can be used for qualitatively correct predictions of the main site for nucleophilic attack, but it cannot be used for

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Table 2. Modeling of Neutral S_NAr, HF as Leaving Group[a]

entry	isomer	in vacuo TS[b]	solvent TS[c]	in vacuo σ-complex[d]	solvent σ-complex[e]	in vacuo σ-complex anion[b]	solvent σ-complex anion[c]	experimental
1	Reaction of (**3 in** Figure 1) with ammonia[f]							
	4	0.0 (87)	0.0 (100)	0.0 (98)	0.0 (100)	0.0 (100)	0.0 (100)	(100)
	2	1.5 (13)	3.5 (0.5)	2.5 (2.5)	4.9 (0.0)	8.1 (0)	7.9 (0)	(0)
	3	6.0 (0)	3.9 (0.2)	8.0 (0)	9.9 (0)	12.2 (0)	10.9 (0)	(0)
2	Reaction of (**11**) with ammonia[g]							
	2	0.0 (100)	0.0 (85)	0.0 (100)	0.0 (89)	0.1 (61)	1.1 (22)	0.1 (61)
	4	8.7 (0)	0.6 (15)	9.9 (0)	0.8 (11)	0.0 (39)	0.0 (78)	0.0 (39)
	3	*h*	*h*	15.5 (0)	13.1 (0)	16.6 (0)	16.6 (0)	(0)
3	Reaction of (**12**) with ammonia[f]							
	4	0.0 (70)	0.0 (96)	0.0 (92)	0.0 (100)	0.0 (100)	0.0 (100)	(100)
	3	0.5 (30)	1.8 (4.5)	1.4 (8)	5.0 (0)	8.2 (0)	6.4 (0)	(0)
4	Reaction of (**13**) with ammonia[f]							
	4	0.0 (89)	0.0 (54)	0.0 (96)	0.0 (85)	0.0 (99)	0.0 (98)	0.0 (67)
	6	2.0 (3)	0.1 (45)	2.2 (2)	1.0 (15)	2.7 (1)	2.3 (2)	0.4 (33)
	5	9.7 (0)	3.0 (0.3)	13.6 (0)	12.6 (0)	14.1 (0)	8.8 (0)	(0)
	2	1.4 (8)	3.1 (0.3)	2.4 (1.5)	5.4 (0)	7.4 (0)	7.9 (0)	(0)
5	Reaction of (**14**) with ammonia[i]							
	2	0.0 (100)	0.0 (82)	0.0 (100)	0.0 (56)	1.4 (4)	2.2 (1)	0.0 (88)
	4	4.4 (0)	1.2 (18)	4.3 (0)	0.5 (44)	0.0 (96)	0.0 (99)	1.4 (12)
6	Reaction of (**8 in** Figure 1) with dimethylamine[j]							
	2	2.3 (1.5)	0.8 (20)	*h*	*h*	0.0 (93)	0.0 (99)	0.0 (80)
	6	0.0 (65)	2.0 (2.5)	*h*	*h*	4.8 (0)	6.4 (0)	1.1 (12)
	3	0.4 (33)	0.0 (78)	*h*	*h*	1.5 (7)	2.7 (1)	1.3 (8)
7	Reaction of (**15**) with (**16**)[k]							
	4	*h*	*h*	0.0 (2.5)	0.0 (89)	0.0 (91)	0.0 (100)	0.0 (75)
	2	*h*	*h*	−2.3 (98)	1.3 (11)	1.4 (9)	4.9 (0)	0.7 (25)
	3	*h*	*h*	6.5 (0)	11.9 (0)	15.1 (0)	18.4 (0)	(0)
	5	*h*	*h*	11.4 (0)	15.8 (0)	*h*	*h*	(0)

[a]Relative energies are given in kcal/mol; isomer distributions are given in %, in parentheses. The compound numbers in bold refer to Figure 2, unless otherwise stated. The calculated isomer distributions have been adjusted for degenerate positions. Experimental relative activation energies were deduced from the product distribution. [b]Structures found by optimization in vacuo.[19] [c]A posteriori single point with the PBF solvent model.[19] [d]The in vacuo energies are based on the structures found by optimization in solvent.[19] [e]Structures found by optimization within the PBF solvent model.[19] [f]Ammonia in 60/40 (v/v) dioxin/water at 25 °C[41] [g]Ammonia in nitromethane, no temperature given.[36] [h]The isomer could not be found or had unreasonable structure. [i]Ammonia in ethanol at 0 °C.[42] [j]Excess dimethylamine in methanol at rt.[43] [k]Tetramethylguanidine in diethyl ether, reflux (34 °C).[37]

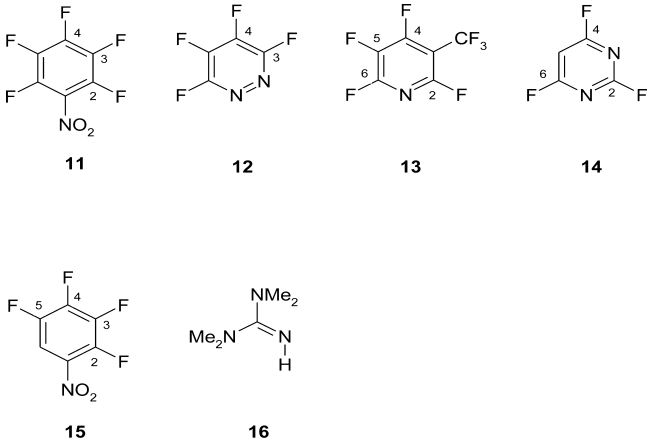

Figure 2. Schematic diagram of the structures studied in Table 2, also showing the labeling of positions.

quantitative predicitions. The results do not support that an anionic σ-complex is involved in the rate determining step of the reaction.

In the previous case (anionic nucleophiles and F^- as leaving group) as well as in similar approaches for S_EAr reactions,[16] the additional solvation calculation has given a slight improvement to the results. In contrast, the solvation correction used for neutral nucleophiles with HF as leaving group, both with the σ-complex approach and with the TS approach, is usually crucial in order to get a quantitatively useful prediction. The reason is probably that for zwitterionic σ-complex, a correct representation of the solvation effects is necessary for reproducing the electronic structure.

It should be noted that entry 7 (Table 2) gives a quantitatively useful prediction even though the experimental data is from a nonpolar solvent; the structures were found by optimization in water, which was followed by an a-posteriori single point solvent calculation in diethyl ether. One can, however, not expect this kind of simple PCM calculation to be adequate for predicting changes in reaction rates (or regioisomeric ratios) when the solvent is changed. In a recent work, Acevedo and Jorgensen studied the S_NAr reaction between the azide anion and 4-fluoronitrobenzene.[44] They could not predict the experimentally observed rate increase in going from protic to dipolar aprotic solvents by using DFT/PCM calculations, but QM/MM Monte Carlo simulations gave useful results.[44] In another paper, Wang and co-workers reported that the regiochemistry of the S_NAr reaction between secondary amines and different electron-deficient difluoroarenes was highly affected by the hydrogen bond basicity of the

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used solvent.[45] Including these types of effects in regioisomeric predictions is obviously beyond the capabilities of PCM.

Anionic Nucleophiles with Cl^-/Br^- as Leaving Group. As anticipated, we could not find any reasonable σ-complex structures for the investigated cases with Cl^- or Br^- as leaving group; none of our polychlorinated or polybrominated entries in Table 3 can be regarded as highly stabilized. Neither geometry optimization in vacuo nor directly in polar solvent (water) gave reasonable σ-complex structures, even when larger basis sets or different softwares[19,20] were used.

The difficulties in finding σ-complex structures prompted us to use a TS approach. These structures could be found by TS optimization directly in solvent.[46] The bond lengths, angles, and the nature of the imaginary vibration of these structures indicate a concerted substitution step, and a typical example of an optimized TS structure is shown in Figure 3. The structures are typical of an early TS, and the normal mode vibration corresponding to the imaginary frequency is for each isomer of the correct character. The comparatively small value of the imaginary frequency (typically 120 cm^{-1}) indicates that the potential energy surface is rather flat in the vicinity of the TS.

Table 3. Modeling of Anionic S_NAr, Cl/Br as Leaving Group[a]

entry	isomer	in vacuo TS[b]	solvent TS[c]	experimental
1	Reaction of (**17**) with the anion of methanol[d]			
	4	0.0 (98)	0.0 (68)	0.0 (65)
	2	2.7 (2)	0.5 (32)	0.4 (35)
2	Reaction of (**18**) with the anion of methanol[e]			
	4	0.0 (99)	0.0 (58)	0.0 (76)
	2	2.6 (1)	0.2 (42)	0.7 (24)
3	Reaction of (**19**) with the anion of methanol[e]			
	4	0.0 (98)	0.0 (77)	1.4 (8)
	2	2.4 (2)	0.7 (23)	0.0 (92)
4	Reaction of (**20**) with the anion of methanol[f]			
	4	2.2 (1)	0.0 (78)	0.0 (85)
	2	9.3 (0)	1.2 (20)	1.4 (15)
	3	0.0 (99)	2.5 (2)	(0)
5	Reaction of (**21**) with the anion of methanol[g]			
	4	0.0 (29)	0.0 (63)	0.0 (57.6)
	2	0.4 (29)	0.7 (37)	0.6 (42.4)
	3	0.2 (42)	3.4 (0.4)	(0)
6	Reaction of (**22**) with the anion of methanol[h]			
	4	1.9 (3.5)	0.2 (19)	0.3 (20.6)
	2	0.0 (88)	0.0 (48)	0.5 (28.6)
	3	1.8 (8.5)	0.3 (33)	0.0 (50.7)
7	Reaction of (**23**) with the anion of H_2S (hydrosulfide)[i]			
	4	0.0 (97)	0.0 (89)	(100)
	2	2.3 (2.5)	1.5 (11)	(0)
	3	3.7 (0.2)	4.4 (0)	(0)
8	Reaction of (**24**) with the anion of methanol[j]			
	4	0.3 (21)	0.5 (18)	(0)
	2	1.0 (17)	1.4 (11)	(0)
	3	0.0 (62)	0.0 (71)	(100)

[a]Relative energies are given in kcal/mol; isomer distributions are given in %, in parentheses. The compound numbers in bold refer to Figure 4. The calculated isomer distributions have been adjusted for degenerate positions. Experimental relative activation energies were deduced from the product distribution. [b]The in vacuo energies are based on the structures found by optimization in solvent.[20] [c]Structures found by optimization within the IEFPCM solvent model.[20] [d]Methanol and potassium hydroxide, reflux 2 h.[50] [e]Methoxide anion, no reaction temperature given[51] [f]Potassium methoxide in methanol. No reaction temperature given.[52] [g]In pyridine at 25 °C.[53] [h]In pyridine at 115 °C.[53] [i]H_2S and KOH in a 30/1 volume mixture of ethanol/water at −5 °C.[54] [j]Methanolic sodium methoxide in pyridine at reflux.[55]

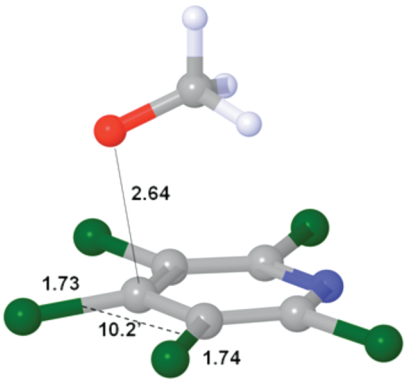

Figure 3. Typical transition state structure (from Table 3, entry 4, position 4).

The molecules used for this case are shown schematically in Figure 4.[47] Relative energies and regioisomer ratios for the investigated systems are shown in Table 3. The results with this method are in good agreement with experimentally determined isomer distributions. The mean average deviation is 0.9 kcal/mol, and quantitatively correct predictions can be made using this approach. We have also calculated the relative energies of some of the final products in order to investigate kinetic versus thermodynamic control. They do not correlate at all with the experimentally found regioisomer distributions, which support our assumption of kinetic control. As for Table 1, one of the entries in Table 3 (entry 3) has a considerable absolute deviation between the solvent calculation and experiment. Also in this case, the absolute deviation is larger for the corresponding in vacuo calculation, and it is likely that explicit solvent molecules in the calculations would be necessary to further improve the prediction.

To the best of our knowledge, there is no conclusive experimental evidence supporting a concerted or stepwise mechanism for S_NAr reactions with Cl^- or Br^- as leaving groups. The only experimental work done on establishing the nature of the reaction intermediate with Cl or Br as leaving groups are cases where the intermediate is highly stabilized, for example, in the nucleophilic substitution of OH^- with 2,4,6-trinitro-chlorobenzene[48] or 2,4-dinitro-chlorobenzene,[49] cases where the σ-complex has been demonstrated to exist. Nevertheless, the failure of our σ-complex approach and the success of the TS approach is consistent with the theoretical investigations of the nature of the reaction that we discussed in the Introduction.[15,18]

We do not rule out that σ-complex structures with Cl/Br as leaving group exist. Perhaps more elaborate model systems, including explicit solvent molecules and/or counterions, are required to find this stationary point on the potential energy surface. Another possibility is that the potential energy surface is so flat that most S_NAr reactions with anionic nucleophiles and with Cl^- or Br^- as leaving group, unlike those with F^- as leaving group, are in practice concerted. In any case, the difficulties in finding relevant σ-complex structures for these types of reactions make the simplified σ-complex approach unsuitable.

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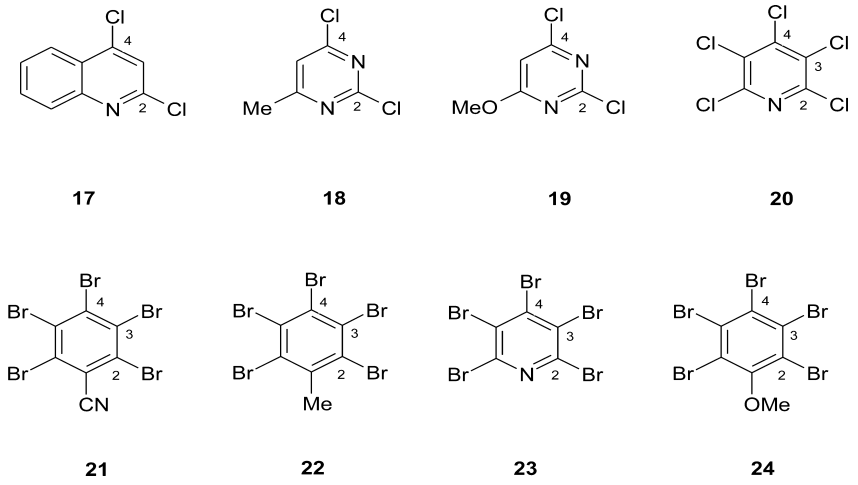

Figure 4. Schematic diagram of the structures studied in Table 3, also showing the labeling of positions.

Neutral Nucleophiles with HCl/HBr as Leaving Group. The situation for this case is similar to the previous one; we were unable to find any relevant σ-complex structures and instead tried the TS approach.[46] Also in this case, the bond lengths and angles of these structures indicate a concerted substitution step; a typical TS structure is shown in Figure 5.

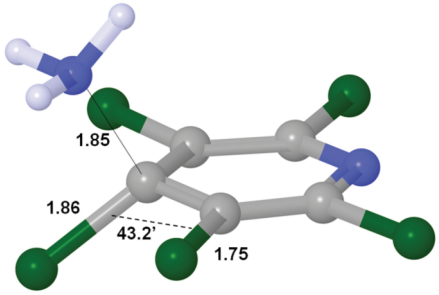

Figure 5. Typical transition state structure (from Table 4, entry 6, position 4).

The molecules investigated for this type of reactions are shown schematically in Figure 6 and in Figure 4. Relative energies and regioisomer ratios for the investigated systems are shown in Table 4. The results with this method show good agreement with experimentally determined isomer distributions. The mean average deviation is 0.7 kcal/mol, and quantitatively correct predictions can be made using this approach.

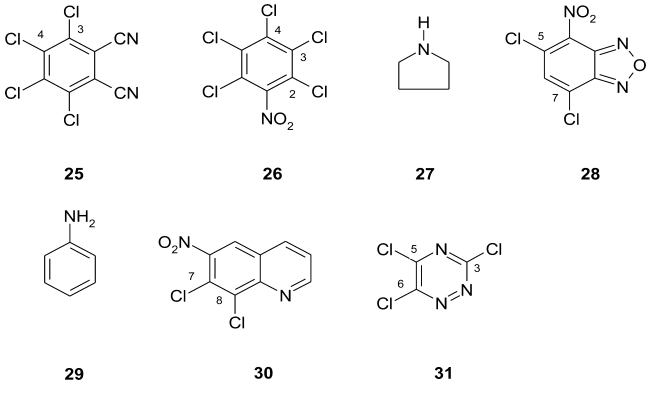

Figure 6. Schematic diagram of the structures studied in Table 4, also showing the labeling of positions.

It is interesting to observe that it is possible to reproduce the experimental observation that the regioisomeric outcome changes when the nucleophile is changed from ammonia to $HNEt_2$ in the reaction with pentachloro-pyridine (Table 4, entry 6 and 7). For entry 7, it was necessary to calculate the energies of several TS conformers in order to obtain a correct prediction. This is the same type of observation that we made with the entries 10 and 11 in Table 1 in the first results section. This type of regioisomeric shift, which depends on the changing of the nucleophile, is of course inherently impossible to predict using a reactivity index model that is based on the ground state properties of the electrophile.

DISCUSSION

The performance of the investigated methods, measured as average absolute deviation,[21] is summarized in Table 5. The quality of the predictions obtained by the investigated methods are of a surprisingly good quality, considering the wide range of solvents and temperature conditions under which the reactions were run and despite having chosen moderate levels of theory and small basis sets. In addition, the approaches used are very straightforward, without elaborate model systems, systematic conformational searches or specific consideration of solvent–solute interactions. There are probably a number of reasons for these surprisingly good results. One is that that there are large error cancellations in this type of relative energy calculation, and they limit the need for highly accurate quantum mechanical methods. Another reason might be that that the negative charge in the adducts is sufficiently well delocalized to make the simple PCM approach sufficient, and the need for explicit solvent calculations is thus small. A third reason could be that the examples studied in this paper are comparatively small, and rigid systems where high-quality regioisomeric data exist. This makes them less prone to computational errors than large, flexible ones. For example, the B3LYP hybrid functional that we used is known to incorrectly describe dispersion forces.[62] Furthermore, the absence of conformational searches and the representation of the transition state ensemble with only one TS structure is less severe for small and unflexible systems.[63] The use of DFT is also rather insensitive to the size of the basis set; Lynch and co-workers have shown that the addition of

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Table 4. Modeling of Neutral S_NAr, HCl/HBr as Leaving Group[a]

entry	isomer	in vacuo TS[b]	solvent TS[c]	experimental
1	Reaction of (**25**) with ^{t}BuSH[d]			
	4	0.0 (63)	0.0 (96)	(100)
	3	0.3 (37)	1.9 (3.5)	(0)
2	Reaction of (**26**) with (**27**)[e]			
	2	0.0 (100)	0.0 (100)	0.0 (73)
	4	5.9 (0)	3.5 (0.2)	0.2 (27)
	3	6.9 (0)	5.8	(0)
3	Reaction of (**28**) with (**29**)[f]			
	5	0.0 (100)	0.0 (100)	(100)
	7	14.6 (0)	9.1 (0)	(0)
4	Reaction of (**30**) with ammonia[g]			
	7	0.0 (100)	0.0 (100)	(100)
	8	5.4 (0)	5.2 (0)	(0)
5	Reaction of (**31**) with ammonia[h]			
	5	0.0 (100)	0.0 (100)	(100)
	3	3.7 (0.2)	6.2 (0)	(0)
	6	8.4 (0)	10.0 (0)	(0)
6	Reaction of (**20 in** Figure 4) with ammonia[i]			
	4	0.2 (26)	0.0 (70)	0.0 (70)
	2	0.0 (74)	0.9 (30)	0.9 (30)
	3	6.1 (0)	6.4 (0)	(0)
7	Reaction of (**20 in** Figure 4) with $HNEt_2$[i]			
	4	3.4 (0.1)	1.4 (4)	2.3 (1)
	2	0.0 (100)	0.0 (96)	0.0 (99)
	3	9.5 (0)	8.0 (0)	(0)
8	Reaction of (**23 in** Figure 4) with $HNMe_2$[j]			
	4	1.2 (8)	0.7 (15)	0.7 (15)
	2	0.0 (92)	0.0 (85)	0.0 (85)
	3	6.8 (0)	6.4 (0)	(0)

[a]Relative energies are given in kcal/mol; isomer distributions are given in %, in parentheses. The compound numbers in bold refer to Figure 6, unless otherwise stated. The calculated isomer distributions have been adjusted for degenerate positions. Experimental relative activation energies were deduced from the product distribution. [b]The in vacuo energies are based on the structures found by optimization in solvent (6-31+G(d,p) as basis set).[20] [c]Structures found by optimization within the IEFPCM solvent model.[20] [d]DMF at rt with Et_3N as base.[56] [e]Pyrrolidine, in THF at 50 °C, 20 h under high pressure (0.6−0.8 GPa).[57] [f]Aniline in DMF at ambient temperature.[58] [g]NH_3 in EtOH, sealed steel vessel at 160 °C, 24 h.[59] [h]Methanolic ammonia. No temperature given.[60] [i]In ethanol. No temperature given.[52] For entry 7, we used the simplified nucleophile $HNMe_2$ in the calculation instead of the experimentally used $HNEt_2$. [j]In ethanol, reflux.[61]

diffuse functions to a DZ basis set is more important than increasing the basis set to a TZ.[64]

In a synthetic planning situation, the accuracy obtained with these approaches is sufficient to tell the chemists with reasonable certainty that the reaction considered would give predominately the right isomer, a wrong isomer, or a mixture of isomers. It is worth noticing that the inclusion of the solvent PCM calculations in the methods (either as an a posteriori single point calculation or by optimizing the structures directly in solvent) is necessary to obtain an accuracy at this level.

Beside Cl and Br, it is likely that our simplified σ-complex approach would fail also for substrates (that are not highly stabilized) with other leaving groups, where the element bound to the ring is from the third or fourth row in the periodic table, e.g., sulfur leaving groups. Also in such cases, a TS approach would be necessary to obtain quantitatively correct predictions of regioisomeric outcome.

Table 5. Accuracy of the Methods

	no. of reactions	average absolute deviation in vacuo (kcal/mol)	average absolute deviation in solvent (kcal/mol)
Anionic nucleophiles with F as leaving group			
σ-complex approach	12	1.0[a]	0.6[a]
Neutral nucleophiles with HF as leaving group			
σ-complex approach	6	2.2[b]	0.5[b]
TS approach	6	2.5[a]	0.6[a]
anionic σ-complex	7	1.2[a]	1.9[a]
Anionic nucleophiles with Cl/Br as leaving group			
σ-complex approach		not possible to apply	not possible to apply
TS approach	8	2.3[b]	0.9[b]
Neutral nucleophiles with HCl/HBr as leaving group			
σ-complex approach		not possible to apply	not possible to apply
TS approach	8	1.1[b]	0.7[b]

[a]Structure optimized in vacuo. [b]Structure optimized in solvent.

■ ASSOCIATED CONTENT

Supporting Information

All of the optimized structures and electronic in vacuo energies as well as a worked through example of how the average absolute deviations have been computed. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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