Theoretical Study on the Structural Properties of Various Solvated Metalated 3-Halo-1-azaallylic Anions

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Metalated 3-halo-1-azaallylic anions are important building blocks for the preparation of a wide variety of heterocyclic and highly functionalized compounds. A theoretical description of the structural properties of halogenated 1-azaallylic anions in vacuo and in tetrahydrofuran (THF) solution is presented to gain insight into their reactivity behavior. The configurational flexibility of fluorinated and chlorinated 1-azaallylic anions is examined, and it is shown that these anions have far less configurational flexibility as compared with nonhalogenated analogues, with a strong preference to occur as *Z*/anti isomers. In addition, the driving force for transmetalation, that is, the replacement of the lithium cations with K^+, Cu^+, $ZnCl^+$, $CuCl^+$, or $MgBr^+$ is studied. To obtain reliable results, the structures were modeled in THF using the combined implicit/explicit solvent approach resulting in different coordination numbers for lithium in the *Z*/anti and *E*/anti isomers. Calculations on dimerization energies show that coordination with THF is energetically preferred over aggregation.

Introduction

α-Heteroatom-substituted carbanions stabilized by an electron-withdrawing group (acyl, alkoxycarbonyl, sulfonyl, sulfinyl, cyano, carbamoyl) have been used intensively as synthetic building blocks for the synthesis of various organic compounds, including a wide variety of azaheterocyclic compounds.[1] However, one combination appears to be unsuccessful when a halogen and an acyl group are combined. This is due to the instability and nonselective reactivity of *β*-haloenolates **2**. (See Figure 1.)[2,3] A convenient way to overcome these problems is the conversion of α-haloketones **1** toward the corresponding less-reactive α-haloimines **4**. After deprotonation of the latter, the corresponding 1-azaallylic anions **5** can be easily used in different organic transformations.[2−5] In that respect, mainly α-chlorinated imines have been used as precursors for interesting acyclic, carbocyclic, and heterocyclic compounds.[6−16] Whereas the corresponding brominated and iodinated imines are generally more difficult to handle because of their instability,[2,3,9,17] 1-azaallylic anions derived from α-fluorinated imines have been used to study the regioselective deprotonation and stereoselective alkylation[8,18] and have recently proved to be useful building blocks for interesting fluorinated heterocycles.[19] Unfortunately, very little is known about the stereochemistry of chlorinated and fluorinated 1-azaallylic anions, which makes it difficult to understand their behavior in stereoselective reactions such as aldol condensations. A thorough investigation and comparison of these fluorinated and chlorinated species will lead to new insight into this matter.

In our previous communication, the *E*-to-*Z* isomerization of lithiated 3-chloro-1-azaallylic anions **7** and **9** (Table 1) in tetrahydrofuran (THF) solution was investigated using quantum mechanical molecular dynamics (QM-MD) and a metadynamics simulation in a periodic box containing 61 THF molecules combined with ROESY-NMR experiments.[20] It was shown that the *Z* isomer **7** is the most stable isomer and that the *Z*-to-*E* isomerization is a highly activated transition that is very unlikely to occur. This was confirmed by NMR experiments demonstrating that only the *Z* isomer **7** is present in solution. Until then, theoretical calculations on chlorinated 1-azaallylic anions had only been performed on heterocyclic lithium azaenolates of chiral oxazolines.[21] The *E* isomer, where the nitrogen, chlorine, and lithium are at the same side of the C=C bond, is therein found to be the most stable isomer. The present study describes an in-depth investigation of the effect of the halogen atom and the metal counterion on the stereochemistry and solvation of a broad range of 1-azaallylic anions. We investigated the influence of the metal counterion by comparing various relevant ions such as Li^+, K^+, Cu^+, $CuCl^+$, $ZnCl^+$, and $MgBr^+$. An overview of all studied structures is given in Table 1.

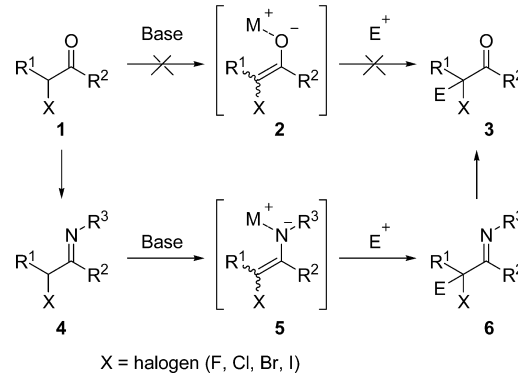

Figure 1. Conversion of α-haloketones **1** to α-haloimines **4** and further to functionalized imines **6** and ketones **3**.

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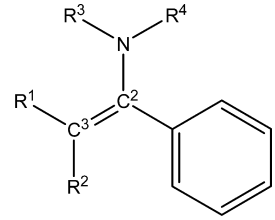
TABLE 1: Overview of the Investigated 3-Halo-1-azaallylic Structures and Their Metal Counter Ions



structure	R^1	R^2	R^3	R^4	structure	R^1	R^2	R^3	R^4
7	Cl	Me	Li^+	^{i}Pr	**21**	Me	F	$ZnCl^+$	^{i}Pr
8	Cl	Me	^{i}Pr	Li^+	**22**	Me	F	^{i}Pr	$ZnCl^+$
9	Me	Cl	Li^+	^{i}Pr	**23**	Cl	F	Li^+	^{i}Pr
10	Me	Cl	^{i}Pr	Li^+	**24**	F	Cl	Li^+	^{i}Pr
11	F	Me	Li^+	^{i}Pr	**25**	Cl	F	$ZnCl^+$	^{i}Pr
12	F	Me	^{i}Pr	Li^+	**26**	F	Cl	$ZnCl^+$	^{i}Pr
13	Me	F	Li^+	^{i}Pr	**27**	Cl	F	K^+	^{i}Pr
14	Me	F	^{i}Pr	Li^+	**28**	F	Cl	K^+	^{i}Pr
15	Cl	Me	$ZnCl^+$	^{i}Pr	**29**	Cl	F	Cu^+	^{i}Pr
16	Cl	Me	^{i}Pr	$ZnCl^+$	**30**	F	Cl	Cu^+	^{i}Pr
17	Me	Cl	$ZnCl^+$	^{i}Pr	**31**	Cl	F	$CuCl^+$	^{i}Pr
18	Me	Cl	^{i}Pr	$ZnCl^+$	**32**	F	Cl	$CuCl^+$	^{i}Pr
19	F	Me	$ZnCl^+$	^{i}Pr	**33**	Cl	F	$MgBr^+$	^{i}Pr
20	F	Me	^{i}Pr	$ZnCl^+$	**34**	F	Cl	$MgBr^+$	^{i}Pr

Little is known about the reactive oligomers of 3-halo-1-azaallylic anions and the mechanisms involved in reactions with electrophiles such as aldehydes. Oligomerization of both lithium enolates[22−26] and nonhalogenated lithium azaenolates[27−29] has been the subject of a large amount of experimental and computational research. However, monomers are found to be the most reactive species in a number of experimental studies.[25,30] By analogy to these experimental findings, mainly monomeric halogenated 1-azaallylic anions will be studied. According to a series of NMR spectra and colligative measurements in THF, both monomeric and dimeric species of 1-azaallylic anions will occur at low concentrations.[31−33] Theoretical calculations are able to provide additional insight into dimerization. Therefore, the possible aggregation into dimeric species is investigated for the lithiated 3-chloro-1-azaallylic anion **7**. It should be noted that it is critical to take the solvent into account properly for all calculations. The influence of solvation with THF will be evaluated because this solvent is most frequently used in reactions with 1-azaallylic anions and because it coordinates with the studied species. The solvent will be treated explicitly via DFT calculations on solvated clusters and implicitly by CPCM calculations.[34]

Computational Details. All computations are performed using the Gaussian03[35] package. The hybrid mPW1PW91[36,37] functional is used as an electronic structure method that is suited for the description of fluoro- and chloroalkyllithium compounds in the gas phase and in ethereal solvents.[22] The double-ζ 6-31$^+$G(d) basis set is used comprising both diffuse and polarization functions for a good description of the oxygen atoms and the ionic character of the species.[34,38] We computed and verified stationary points as well as first-order saddle points by calculating the normal modes. The obtained energies are corrected for the zero-point vibrational energies. The effect of solvation is modeled as the sum of two contributions: one resulting from the coordination of one or more solvent molecules to the solute X (coordination solvation free energy, CSE) and one originating from the bulk solvent effect (dielectric solvation free energy, DSE).[34,39−41] Combination of both contributions allows us to calculate the coordination free energy in solution, ΔG_{sol}, as depicted in Figure 2.

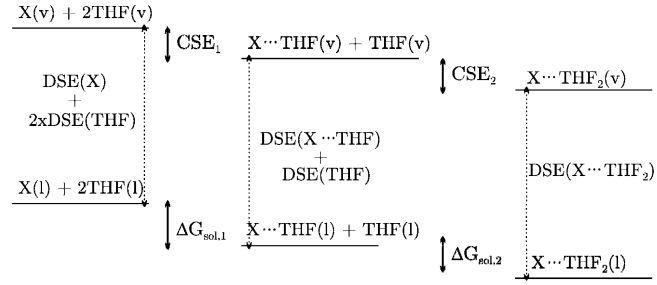


Figure 2. Thermodynamic cycle in two steps for the determination of coordination free energy of species X in solution, ΔG_{sol}, being defined as the driving force for coordination with a THF molecule in solution. The vapor (v) and liquid (l) phase are indicated.

The coordination number of the metal site is determined by requiring a decrease in Gibbs free energy of solvation upon the addition of an explicit solvent molecule.[40] Subsequently, the solvated cluster is embedded in a conductorlike polarizable continuum model (CPCM), and single-point calculations are performed to compute the DSE.[42] The parameter set used for the determination of the cavity in which the system is embedded is crucial for obtaining reliable energies. The standard UA0 method that is implemented in Gaussian03 does not perform properly for ionic species. Therefore, the model based on Pauling radii is used.[43]

Results and Discussion

Configurational Analysis. Because of the importance of lithiated (aza)enolates in organic synthesis,[44−47] 3-fluoro- and 3-chloro-1-azaallylic anions coordinated to lithium are considered at first instance in the present study. For these monohalogenated species **7**−**14**, four isomers can be suggested a priori (Figure 3), each of them characterized by the stereochemistry about the C═C bond (*E* or *Z*) and the position of the *N*-isopropyl group (syn or anti).[27]

The energy scheme in Figure 3 shows that both fluorinated and chlorinated species exhibit a stable global minimum in which the lithium cation and the halogen atom intensely interact. The isomerization process is characterized by two types of internal rotations: amide rotations for syn/anti isomerization (**TS1** and **TS3**) and carbon−carbon double-bond rotations or *E*/*Z* isomerizations (**TS2**). The stable minima for the fluorinated species **11**−**14** are shown in Figure 4, whereas the other structures are shown in the Supporting Information. A remarkable aspect of the energetic minimum is the position of the phenyl group. One would expect this group to be positioned coplanar with the carbon−carbon double bond (the dihedral angle between the C−C double bond and the phenyl ring being equal to zero) to obtain more electron delocalization. The structure, however, does not allow this kind of conformation because of steric hindrance of the phenyl group with the methyl and isopropyl group on the adjacent carbon and nitrogen atoms, respectively, resulting in a dihedral angle of 71° for structure **11.**

Amide C−N bond rotation has been investigated in a number of papers, and a rotational barrier in the range of about 6−100 kJ/mol was found, depending on the nature of the amide.[48−54] The values found here fall within that experimental range. The activation energy for the rotation via **TS1** is quite high, which can be ascribed to the lithium−halogen interaction. The *Z*/syn-to-*E*/syn isomerization in 3-halo-1-azaallylic anions via **TS2** requires a huge amount of energy, whereas in nonhalogenated 1-azaallylic anions, this isomerization is known to occur quite easily.[27,55]

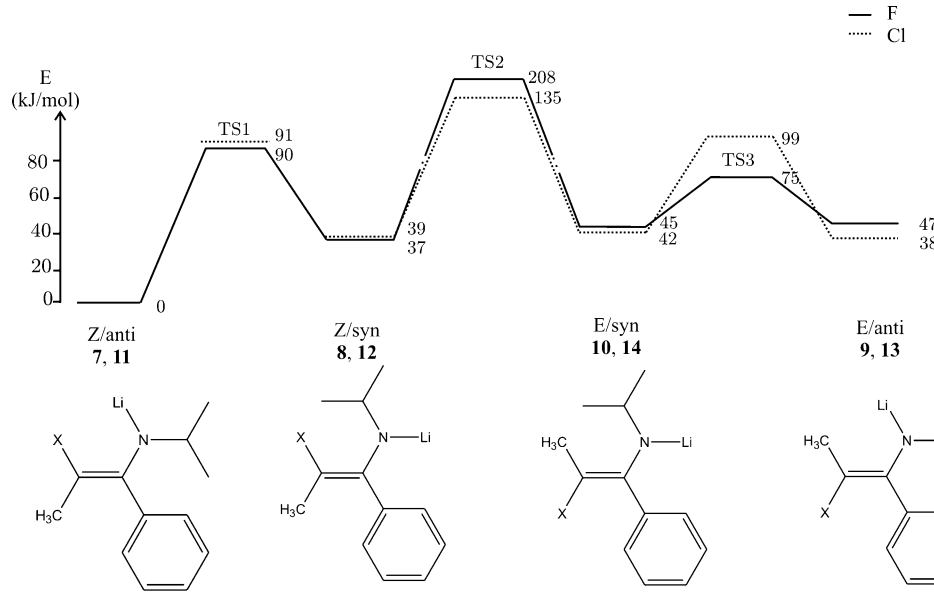


Figure 3. Energy profile for the conformational analysis of chlorinated species **7**−**10** (X = Cl) and fluorinated species **11**−**14** (X = F). The transition-state structures **TS1**−**TS3** for both halogen substituents can be found in the Supporting Information.

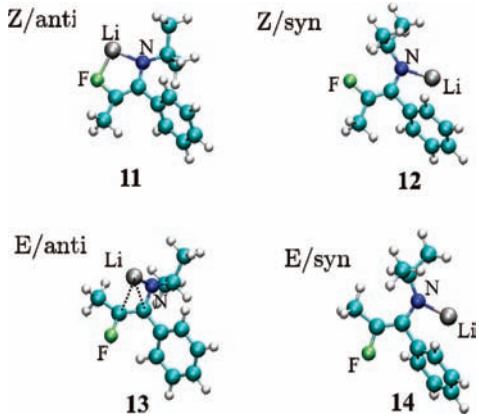


Figure 4. Optimized geometries for lithiated 3-fluoro-1-azaallylic species **11**−**14**.

Because of the strong interaction between fluorine or chlorine and lithium, no barrier could be found in vacuo for the rotation from *Z*/anti to *E*/anti. The latter structure exists as two energetically equivalent enantiomeric structures in which the lithium cation is pyramidally η^3 coordinated (species **13** in Figure 4). This type of coordination was already reported in previous studies of 1-azaallylic anions[21,27] and is a result of the repulsive interaction between Li^+ and the methyl group directing the metal out of plane toward the π cloud of the carbon−carbon double bond.

Solvation in Tetrahydrofuran. The previous results were all obtained in the gas phase, although the investigated species are known to be stabilized by the solvent. We will determine the coordination number of the lithium cation by solvating the 3-halo-1-azaallylic anions using the combined implicit/explicit solvent approach. The free energy decrease in solvation is the result of a coordination free energy (CSE) and a dielectric free energy (DSE). The global free energy of solvation, ΔG_{sol}, can be calculated from the scheme in Figure 2, and the numerical values are shown in Table 2. We will focus on the *Z*/anti isomers in solution because these were found to be the most stable isomers, as shown by the calculations described above, and because the stereochemistry about the C−C double bond is important for the stereochemical outcome of reactions, the *E*/anti isomers will also be considered. Next to lithium, zinc chloride will also be considered because this counterion has a different sterical nature, bearing the chlorine ligand.

The lithiated 3-halo-1-azaallylic anions **7**, **9**, **11**, and **13** always coordinate with at least one THF molecule because of the favorable lithium−oxygen interaction. The coordination with a second THF molecule is generally less favored. Intuitively, the solvation of the *E* isomers **9** and **13** by a second THF molecule should be more favorable compared with the *Z* isomers **7** and **11** because the former isomers lack a halogen−lithium interaction. This is indeed the case. One must notice however, that some values for the second solvation are very close to zero and are probably smaller than the error for these single-point CPCM calculations. The solvated structure of the *E* and *Z* isomers of the 3-chloro-1-azaallylic anions obtained via the explicit/implicit solvent approach is the same as the structure we obtained from ab initio molecular dynamics simulations.[20] For all of the discussed structures, the preferable coordination of the counterion is highlighted in Table 2. For lithium-coordinated species, monosolvated structures are found. The slightly negative $\Delta G_{sol,2}$ for *E*/anti isomers shows a very modest tendency to coordinate with two THF molecules. This finding corresponds with the previously reported molecular dynamics results.[20]

Because $ZnCl^+$ has different characteristics compared with Li^+, the solvation properties of zincated 3-halo-1-azaallylic anions **15**, **17**, **19**, and **21** are also quite different. The chlorine in the $ZnCl^+$ counterion accounts for an important sterical effect. No THF molecule can coordinate with the *Z* isomers **15** and **19**. However, the *E* isomers **17** and **21** do form a solvated complex because of the absence of halogen−zinc interactions. In summary, we find that the zinc counterion in the *Z*/anti isomer does not coordinate with a THF molecule because of steric constraints, whereas the coordination number of zinc in the *E*/anti isomer is one.

The monosolvated structures are shown in Figure 5. The structures differ very little from the ones calculated in vacuo, but the energy difference between the *E* and *Z* isomers is significantly influenced. In Table 3, the energetic preference for the *Z* isomers (ΔG_Z) of the studied species is tabulated as the difference in energy of the *Z* isomer and the *E* isomer. In all cases, the *Z* isomer is the

TABLE 2: Coordination Solvation Energy and Solvation Free Energy for Mono- and Bisolvated Structures Using the Implicit/Explicit Solvation Model for the Anti Configuration of Lithiated and Zincated Complexes[a]

		Lithium					Zinc			
halogen	isomer	nr	CSE_1	$\Delta G_{sol,1}$	CSE_2	$\Delta G_{sol,2}$	nr	CSE_1	$\Delta G_{sol,1}$	CSE_2	$\Delta G_{sol,2}$
F	Z/*anti*	**11**	-75.1	-3.5	-39.7	-0.2	**19**	-49.5	8.1	-13.1	16.4
	E/*anti*	**13**	-83.2	-9.2	-45.7	-2.3	**21**	-56.5	-17.5	-23.8	12.7
Cl	Z/*anti*	**7**	-75.1	-14.7	-37.7	12.7	**15**	-47.8	2.7	9.5	48.8
	E/*anti*	**9**	-83.3	-10.0	-40.8	-0.5	**17**	-58.4	-20.1	-19.9	10.12

[a] All values are in kilojoules per mole. Preferred interactions are highlighted in grey, showing the coordination number of the studied species.

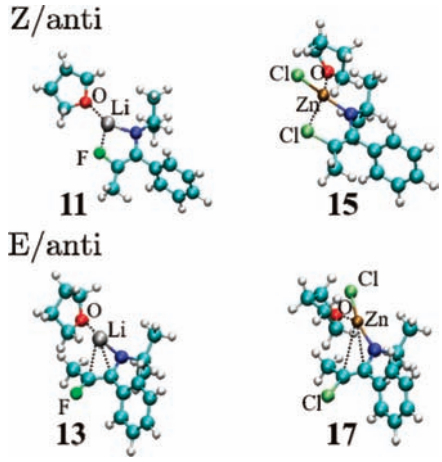


Figure 5. Monosolvated geometries of lithiated 3-fluoro-1-azaallylic anions **11** and **13** and zincated 3-chloro-1-azaallylic anions **15** and **17**.

TABLE 3: *Z* Preference Energy, ΔG_Z (kJ/mol), for the Anti Isomers of 3-Halo-1-azaallylic Anions in Vacuo and in the Implicit/Explicit Solvent Model for THF

Z vs *E* isomer	halogen	counterion	in vacuo ΔG_Z	in solvent ΔG_Z
7 vs **9**	Cl	Li^+	−38.02	−41.19
15 vs **17**	Cl	$ZnCl^+$	−41.47	−31.99
11 vs **13**	F	Li^+	−46.99	−27.72
19 vs **21**	F	$ZnCl^+$	−27.41	−18.83

most stable one. This is the result of the repulsive interaction between the halogen and the π cloud of the phenyl substituent in the *E* isomers (**9**, **13**, **17**, **21**) and the attractive interaction between the metal cation and the halogen atom in the *Z* isomers (**7**, **11**, **15**, **19**). Table 3 also shows that ΔG_Z is dependent on both the halogen and the counterion.

Transmetalation. In general, 3-halo-1-azaallylic anions **5** are mostly synthesized using lithium diisopropylamide (LDA) as a base for the deprotonation of the starting imines **4**. However, to influence the structural, coordination, and reactivity properties of 1-azaallylic anions[56−58] and to increase the stereoselectivity in organic reactions with these species and related enolates, such as additions across aldehydes[59−64] or imines,[65,66] it can be of considerable benefit to introduce another metal counterion to the anion (as shown above for the zincated 3-chloro-1-azaallylic anion).[58,65,66] The addition of a salt of the desired counterion to the lithiated anions will result in the transmetalation of the starting 3-halo-1-azaallylic anions. In this part, the driving force for the transmetalation reaction will be discussed. A selection of relevant metals was made consisting of K^+, Cu^+, $CuCl^+$, $MgBr^+$, and $ZnCl^+$.

TABLE 4: Metalation Energy ($E_{met} = E_{complex} - E_{metalcation} - E_{anion}$) in the Vapor Phase and the Preference to Interact with Fluorine in Liquid THF for Various Metals[a]

			in vacuo			in solvent
counterion	*Z* isomer	*E* isomer	E^{Cl}_{met}	E^{F}_{met}	ΔE^{vac}_{met}	ΔG^{sol}_{met}
Li^+	**23**	**24**	−649.3	−659.6	−10.3	−13.2
$ZnCl^+$	**25**	**26**	−963.3	−960.7	2.7	2.0
K^+	**27**	**28**	−458.7	−466.1	−7.5	−10.8
Cu^+	**29**	**30**	−780.6	−766.5	14.1	−0.9
$CuCl^+$	**31**	**32**	−1018.5	−1015.3	3.1	1.2
$MgBr^+$	**33**	**34**	−890.9	−900.9	−10.1	−13.0

[a] Preference for the metal to interact with fluorine is given in vacuo (energetic difference, $\Delta E^{vac}_{met} = E^{F}_{met} - E^{Cl}_{met}$) and in the implicit/explicit solvent model (Gibbs free energy difference, ΔG^{sol}_{met}). All values are in kilojoules per mole, and all structures were optimized to obtain the presented energies.

To assess both the chlorine−metal and the fluorine−metal interactions, the 3-chloro-3-fluoro-1-azaallylic anions **23**−**34** are studied. Moreover, these species are synthetically interesting because it has been shown that 3,3-dihalogenated-1-azaallylic anions can be used for the synthesis of a variety of dihalogenated heterocycles such as piperidines[19] and azetidines;[2,67−69] therefore, 3-chloro-3-fluoro-1-azaallylic anions can also be useful as versatile building blocks. For this kind of applications, like in the previous section, the stereoselectivity of the reactions will be determined by the stereochemistry about the C−C double bond. For every metal complex, the metalation energy E_{met} (Table 4) can be determined resulting from metal−chlorine complexation in the *Z*/anti isomers (E^{Cl}_{met}) and metal−fluorine complexation in the *E*/anti isomers (E^{F}_{met}). This number quantifies the difference in the interaction strength of the metal with fluorine and chlorine.

Transmetalation of lithiated 1-azaallylic anions to their zincated analogues by the addition of $ZnCl_2$ is known to occur easily.[44−47] The conversion of lithiated 1-azaallylic anions to their Cu^+(I) analogues using CuI[70] or CuCN[71] is also reported in the literature. The increase in the absolute value of the metalation energy is the driving force for this metal exchange reaction. Indeed, $ZnCl^+$ and Cu^+ interact stronger than Li^+ with the 3-halo-1-azaallylic anion.

The coordination energy difference in vacuo between the *E* and *Z* isomers is expressed as $\Delta E^{vac}_{met} = E^{F}_{met} - E^{Cl}_{met}$ and expresses the relative preference of the metal to interact with fluorine. (See Table 4.) The free energy difference in vacuo in combination with the CPCM energies results in the total free energy difference in solution between the *E* and *Z* isomers, ΔG^{sol}_{met}. If the values of ΔE^{vac}_{met} and ΔG^{sol}_{met} are negative, then the metal will coordinate more strongly with fluorine than with chlorine. Group I and II metals (Li^+, K^+, and $MgBr^+$) tend to interact more strongly with

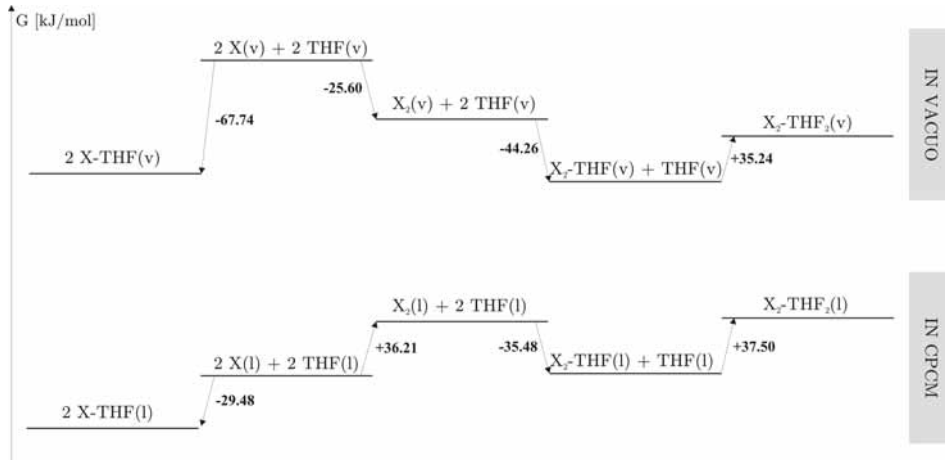


Figure 6. Thermodynamic cycle for the determination of the Gibbs free energy difference between the dimer of the lithiated 3-chloro-3-methyl-1-azaallylic anion **7** (X_2) and the solvated species (X-THF) using the implicit/explicit solvent model. All energy values are in kilojoules per mole.

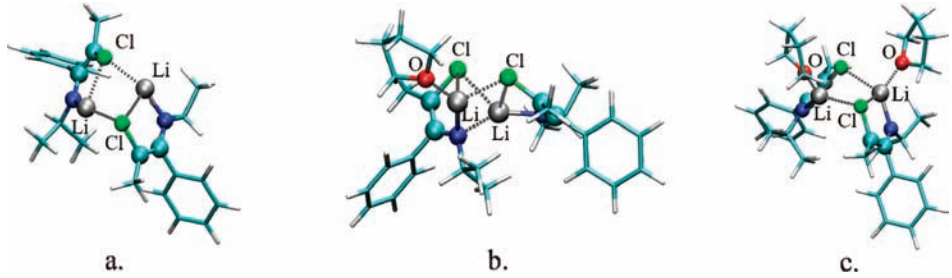


Figure 7. Optimized structures for (a) the dimer, (b) the monosolvated dimer, and (c) the bisolvated dimer of species **7**.

fluorine, resulting in a modest *E* preference up to 13.2 kJ/mol. The studied transition metals prefer to interact with the chlorine, but there is only a small difference with fluorine. All of the metals studied, except Cu^+(I), need just one THF molecule to be fully solvated. The numerical values for the CSE and DSE can be found in the Supporting Information. In most cases, solvation alters the difference in metalation energy only slightly. In the case of monovalent Cu^+(I) cations, a large solvent effect due to the implicit solvent model is observed.

Aggregation. The aggregation of (lithium) enolates has been the subject of various papers revealing that the formation of oligomers is of considerable importance.[22,24,27] Other studies indicate that, although the formation of di-, tri-, or tetramers occurs, the monomers are the reactive species.[25,30] To assess the importance of aggregation relative to solvation, we performed calculations on the dimer (X_2) of the lithiated 3-chloro-3-methyl-1-azaallylic anion **7**. In Figure 6, the Gibbs free energy profile for solvation and dimerization is shown using an implicit/explicit solvent model analogous to the method described in the previous section. The dimeric structure with and without solvation is shown in Figure 7. In the vapor phase, the solvated monomer (X-THF(v)) and the solvated dimer (X_2-THF(v), Figure 6) are almost isoenergetic, indicating an equilibrium between both structures. When including long-range solvent effects using the CPCM model, the energetic scheme is totally altered, making only the monosolvated monomers (X-THF(l)) feasible in solution. These results might seem to contradict the broad range of published papers in which oligomerization of the analogous enolates readily occurs. However, it can be reasonably understood why the 3-halo-1-azaallylic anions are less prone to aggregation in solution.

In contrast with previously reported studies of nonhalogenated enolates, the presence of the α-halogen substituent in the studied azaenolates enables an intramolecular, stabilizing interaction between the lithium cation and the halogen. This interaction leads to a higher degree of coordinative saturation of the metal[72] and reduces the driving force for aggregation or solvation compared with non-α-halogenated enolates.[25] The results in Figure 6 also show that the interaction energy between lithium and the THF oxygen atom is higher as compared with the dimerization energy, resulting in a preference for solvation rather than dimerization. These calculations indicate that monomeric species will be predominantly present in a THF solution and are therefore worthwhile to investigate.

Conclusions

The theoretical calculations show that the preferred configuration of metalated 3-halo-1-azaallylic anions comprises the anti orientation of the *N*-alkyl substituent with regard to the carbon−carbon double bond and the *Z* configuration, where the nitrogen and halogen are positioned at the same side of the carbon−carbon double bond. These results are valid for both fluorinated and chlorinated 1-azaallylic anions and for a broad range of metal cations. A strong interaction was found between the solvent and the metal center, suggesting a considerable role in the reactivity of 1-azaallylic anions toward electrophiles because the solvent influences the steric environment of the reactive centers. Therefore, the embedding of a solvated cluster in a continuum model is necessary for obtaining a more accurate description of the solvent surroundings and more reliable energies in solution. In addition, it is shown that 3-chloro-3-methyl-1-azaallylic anions interact more strongly with THF than with themselves, indicating that mainly monomeric species are present in solutions. The driving force for transmetalation was assessed for a range of different metal cations. Depending on the application, different metal cations can be

selected to perform stereoselective organic reactions with the studied 3-halo-1-azaallylic anions.

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Supporting Information Available: Optimized geometries in *xyz* coordinates and absolute energies of all species. This material is available free of charge via the Internet at http://pubs.acs.org.

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