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Insight into the Solvation and Isomerization of 3-Halo-1-azaallylic Anions from Ab Initio Metadynamics Calculations and NMR Experiments

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In organic synthesis, it is observed experimentally that the nature of the solvent can influence tremendously the reactivity and overall product selectivity. In this communication, we report on the *E*/*Z* isomerization of a typical solvated species, that is, the stable lithiated 3-chloro-3-methyl-1-azaallylic anion readily accessible from the *N*-isopropylimine of α-chloropropiophenone, from a theoretical and a subsequent NMR study. To date, the configurational properties of these 3-chloro-3-methyl-1-azaallylic anions are poorly understood. Our main emphasis is devoted to the monomeric species as these are believed to be the most important for further reactivity studies (see below). It will be shown that the investigated species is a particular example in which the inclusion of the solvent in the modeling study is of the utmost importance to determine the proper chemical behavior.

The 3-chloro-3-methyl-1-azaallylic anion was chosen as a model compound to obtain a deeper insight into the structural features of 3-halo-1-azaallylic anions and to get a better understanding, and eventually a better control, of the stereochemical outcome of the reactions in which these anions are involved. Since their first use in the early 1960s,[1–3] non-halogenated 1-azaallylic anions have gained a predominant role in organic synthesis due to their ability to form new C–C bonds with a lack of side products.[4] The chemistry of 1-azaallylic anions leads to basic heterocyclic systems such as aziridines, azetidines, pyrrolidines, pyrroles, piperidines, oxiranes, oxolanes, and higher functionalized ring systems, currently of interest for pharmaceutical chemistry and agrochemistry. The application of certain halogenated counterparts, that is, the 3-chloro-3-methyl-1-azaallylic anions, in particular by the group of De Kimpe and more general by the group of Florio, which incorporated the 3-chloro-3-methyl-1-azaallylic moiety into heterocyclic structures, has led to the synthesis of various important classes of compounds such as cyclopropanes,[5] tetrahydrofurans,[6] tetrahydropyrans,[6c] oxiranes,[7] aziridines,[7b,d,8] chloroimines,[9] pyrroles and pyridines,[10] steroids,[11] alkenylheterocycles,[12] and oxazetidines.[13] As mentioned, 3-chloro-3-methyl-1-azaallylic anions can be used for the synthesis of functionalized oxiranes and aziridines since the former anions behave as nucleophiles in Darzens- and aza-Darzens-type reactions with carbonyl compounds and imines.[7,8] One of the determining factors in the stereochemical outcome of these Darzens-type reactions is the *E*/*Z* stereochemistry of the starting 1-azaallylic anion.[14] Therefore, it is important to know and understand the configurational properties of 3-chloro-3-methyl-1-azaallylic anions in order to perform aldol- and Mannich-type reactions with these intermediates in a stereocontrolled manner.

NMR investigation and semiempirical calculations on the stereochemistry of (2-(α-chloroethyl)benzothiazolyl)lithium and (4,4-dimethyl-2-(α-chloroethyl)oxazolinyl)lithium have demonstrated that internal coordination between lithium and chlorine stabilizes the corresponding isomer with nitrogen and chlorine at the same side of the C=C double bond.[15] The lack of such structural investigations on 3-chloro-3-methyl-1-azaallylic anions in sensu stricto urged us to study their stereochemical properties.

The *E*/*Z* isomerism for non-halogenated 1-azaallylic anions has been observed and investigated quite frequently. The facile carbon–carbon bond rotation in simple lithiated 1-azaallylic anions was investigated using ^{1}H NMR spectros-

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copy.[16] The rotational activation free energy was found to be (74.1 ± 1.3) kJ mol^{-1} at 313 K. *E*/*Z* isomerization was also observed upon deprotonation of ketimines of 2-butanone at room temperature.[17] For closely related non-chlorinated analogues of the species **1**–**2** in Figure 1, that is, the lithiated anion derived from the *N*-phenylimine of propiophenone, isomerization from the kinetically favored *E* isomer with the methyl group and the phenyl group at the same side of the C2=C3 double bond (like in *Z*-isomer **1**) to the thermodynamically most stable *Z* isomer with the methyl group and nitrogen at the same side of the C2=C3 double bond (like in *E*-isomer **2**), was observed.[18] Therefore, it was assumed that the lithiated 3-chloro-1-azaallylic anions of the present work could also undergo a similar type of isomerization.

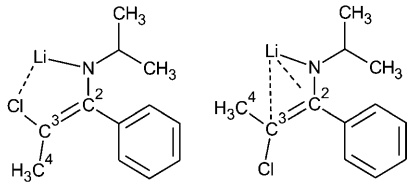

Figure 1. *Z*-isomer **1** and *E*-isomer **2** of the lithiated (2-chloro-1-phenylprop-1-en-1-yl)isopropylamide anion.

At first instance, the lithiated 3-chloro-3-methyl-1-azaallylic anion was generated by deprotonation of *N*-(2-chloro-1-phenylpropylidene)isopropylamine with lithium diisopropylamide (LDA) in [D_8]THF at 273 K and analyzed by ^{1}H and ^{13}C NMR spectroscopy. The α-chloropropiophenone imine was deprotonated under these conditions to a single stereoisomer as demonstrated by the presence of a single set of characteristic ^{1}H NMR chemical shifts of the methyl group on the double bond (s, $\delta = 1.77$ ppm), methine function (septet, 2.96 ppm) and isopropyl methyl groups (d, 0.83 ppm). Also a single set of characteristic ^{13}C NMR chemical shifts of the lithiated 3-chloro-1-azaallylic anion were observed (see Supporting Information). The stereochemistry of the *Z* anion **1** was determined by off-resonance ROESY spectroscopy showing ROE effects between the methyl group and the *ortho*-protons of the phenyl ring positioned at the same side of the carbon–carbon double bond (Figure 2). Furthermore, the observed ROE effects between the *N*-isopropyl substituent and the phenyl group support the *anti* stereochemistry of the 3-chloro-1-azaallylic anion, that is, the *N*-isopropyl group is oriented anti with respect to the C2=C3 double bond. In contrast to the non-chlorinated species,[19] the aforementioned NMR experiments indicate that in THF only the *Z*/*anti* isomer **1** occurs and that both amide and C=C double bond rotations are inhibited. This particular behavior of chlorinated 1-azaallylic anions demanded a theoretical interpretation. Before elaborating on the theoretical results, it is important to focus on the tendency of 1-azaallylic anions to form higher aggregates in solution. From the extensive work that has been performed on

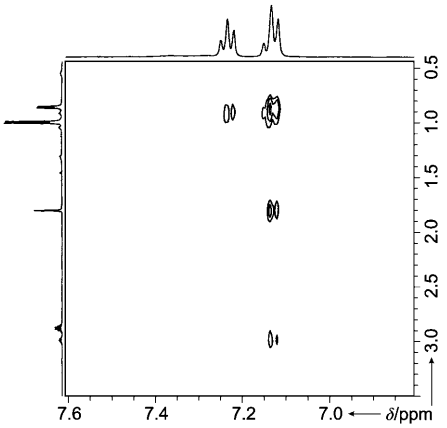

Figure 2. Details of the off-resonance ROESY spectrum of the *Z*-isomer **1** of the lithiated 3-chloro-1-azaallylic anion ([D_8]THF). The resonance signals at 0.96 ppm (doublet) and 2.84 ppm (septet) are from diisopropylamine formed upon protonation of LDA.

lithium 1-azaallylic anions, higher aggregates are also expected here.[19] It must, however, be stressed that the experimental NMR spectroscopy data gives by no means any information on the solution aggregation number of the title compounds. According to a series of NMR spectroscopic studies and colligative measurements in THF, both monomeric and dimeric species will occur at low concentration of the lithium 1-azaallyl anions.[20] On the other hand, the monomeric lithium 1-azaallylic anions retain in most cases their structural properties in the dimer form;[21] the stereochemical preferences in reactions can readily be explained with the properties of the monomeric form.[22] There are also several indications that the monomeric forms are the most likely reactive forms of these molecules. Studies by Streitwieser and co-workers have shown that the reactive form of lithiated compounds, present in solution for the larger extent as higher aggregates, can be the monomeric form due to a kinetic advantage because of lower-energy transition states as compared to the less reactive higher aggregates.[23] Based on these arguments and the expensive computational resources needed for treating higher arguments, the theoretical part of this communication will focus only on the configuration of the monomeric species, being aware that these might be part of higher aggregates under experimental conditions.

Despite the huge amount of theoretical studies that appeared the last years, modeling of complex phenomena such as chemistry in liquids remains a challenge as standard optimization techniques and ab initio molecular dynamics methods are often not suitable.[24,25] The first set of methods is routinely performed nowadays, but for our systems in which the solvent participates actively, a single optimized structure does not resemble the configurational distribution at finite temperature. First-principle molecular dynamics simulations are often restricted by short simulation times. As such, interesting regions of phase space are often so high in free energy that their sampling during a standard MD simulation is a rare event. Enhanced sampling techniques have become

an active research domain.[25] The relatively new metadynamics method has particularly attracted our attention. It was first proposed by Laio and Parrinello and enables an enhanced sampling of separated regions in phase space, simultaneously mapping the underlying free-energy landscape as a function of a limited number of collective variables.[26] The particular implementation is based on the work of Iannuzi et al.[27]

Prior to the modeling of the 1-azaallylic anions, we modeled the liquid structure of pure THF by using first-principle molecular dynamics calculations. The liquid structure of THF was recently assessed via hydrogen/deuterium isotopic substitution neutron-diffraction techniques by Bowron, Finney, and Soper.[28] A periodic cubic simulation cell was filled with 64 THF molecules. This choice represents an optimal compromise between computational cost and a proper embedding of the solute in the solvent. The simulation cell size was chosen to correspond with the experimental density of 0.88 kg dm^{-3}.[29] The performance of the THF model was validated by calculating the radial distribution function (RDF) of the molecular centers, which was found to be in excellent agreement with the benchmark RDF reported in reference [28] (see Supporting Information). Moreover, the MD simulations yielded a conformational distribution of 59% twisted and 41% oxygen envelope, indicating a thorough sampling of the system.[28]

After the THF model had been successfully assessed, it was applied to study the degree of coordination of the 3-chloro-1-azaallylic anions in solution. The coordination number for lithium enolates in ethereal solvents is rather difficult to establish but four-coordinate lithium cations have been clearly recognized in NMR studies of solvent separated ion pairs.[30] For contact ion pairs, coordination is expected less important because of the electrostatic effect of the counter ion. Theoretically the structures of a variety of organic lithium compounds were determined in the gas phase and in solvation using microsolvation with explicit ethereal ligands and/or continuum models.[31] For the 1-azaallylic anions as encountered here which are subject to large steric crowding, the degree of coordination is not a priori clear and can not be deduced straightforwardly from the experimental data. Isothermal–isobaric (NPT) molecular dynamics simulations during a period of 2.5 ps show that the *Z*-isomer **1** is monocoordinated whereas the *E*-isomer **2** features a two-fold coordination with THF (illustrated in Figure 3). In the *E*-isomer **2** the halogen–lithium coordination is not present which allows a second THF molecule to coordinate with the counter ion.

In order to obtain insight into the occurrence of only one stereoisomer in case of 3-chloro-3-methyl-1-azaallylic anions **1** and **2**, we decided to construct the free-energy landscape connecting the basins of the two isomers. To this end we applied the metadynamics method in which the dihedral angles Cl-C3-C2-N and C4-C3-C2-N were chosen as collective variables. This choice guarantees the independent movement of the methyl and chlorine substituents. The resulting free-energy landscape as a function of the two dihedral angles is displayed in Figure 4. The Gibbs free energy barriers for *E*-to-*Z* and *Z*-to-*E* isomerization amount to (107.1 ± 12.1) kJ mol^{-1} and (128.6 ± 12.1) kJ mol^{-1}, respectively.[32] These barriers are high, preventing isomerization at the experimental temperature. The *Z*-isomer **1** is more stable than the *E*-isomer **2** by $\Delta G_{Z-E} = (21.5 \pm 12.1)$ kJ mol^{-1}, which indicates that the experimentally observed *Z*-isomer **1** is thermodynamically favored. Within a static cluster approach using a combined explicit/implicit solvent model we were unable to determine the transition state for *E*/*Z* isomerization as the coordination number varies during the chemical transformation. Moreover, the stability of the *Z*-isomer **1** with respect to the *E*-isomer **2** was 20 kJ mol^{-1} too high compared to the metadynamics calculations. By capturing the movement of both dihedral angles, we were able to observe the sp^2 to sp^3 hybridization transition of the C3 carbon atom upon rotation, a well-known feature of rotations about allylic bonds. This is reflected in the fact that the saddle point, denoted as $(E–Z)^{\ddagger}$, does not lie on the linear pathway connecting both isomers, which confirms a posteriori the importance of capturing the movement of both dihedral angles.

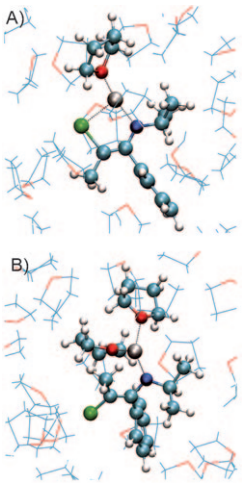

Figure 3. Characteristic snapshot of the MD simulation of the *Z*-isomer **1** (A) and the *E*-isomer **2** (B) solvated in THF.

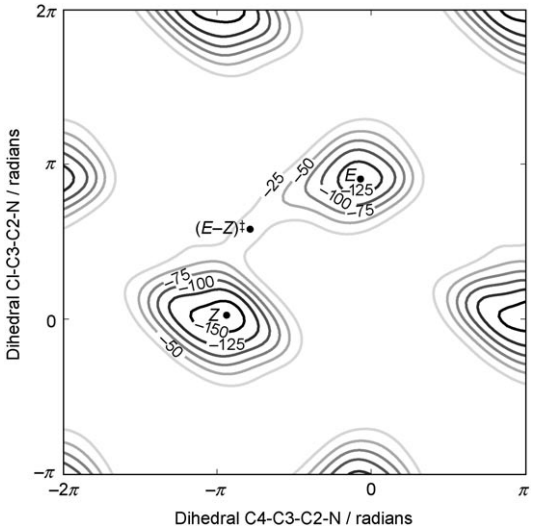

Figure 4. Gibbs free energy profile (in kJ mol^{-1}) governing the *E*–*Z* isomerization of the lithiated 3-chloro-1-azaallylic anion in THF. The positions of both stable isomers *E* (**2**) and *Z* (**1**) and the saddle point $(E–Z)^{\ddagger}$ are added. Note that the two collective variables feature a 2π periodicity.

Finally, we infer from both first principle metadynamics and NMR experiments that the *Z* isomer is the only configuration formed upon the deprotonation of the starting imine to the lithium 3-chloro-1-azaallylic anion. The interaction between the counter ion and the halogen, an effect that is not present in the non-halogenated 1-azaenolates, stabilizes the *Z* isomer by 21 kJ mol^{-1}. Moreover, the transition from the *Z* to the *E* isomer is very highly activated and features a change in coordination for the lithium cation as the broken lithium-chlorine interaction is replaced by a lithium–THF interaction. These effects can only be seen because of the explicit inclusion of the large THF model in the QM simulations. These results show that the stereochemistry of 3-chloro-3-methyl-1-azaallylic anions is manifestly different compared to their non-chlorinated counterparts and is the result of their configurational stability which should be beneficial during their synthetic use as functionalized intermediates in stereoselective reactions.

Experimental Section

All molecular dynamics calculations were performed within the cp2k/quickstep code,[33] employing the Gaussian and plane-wave (GPW) density functional method and periodic boundary conditions. A BLYP[34] gradient-corrected functional was used throughout, together with a TZVP-PSP[35] basis set, a 400 Ry cutoff for the auxiliary plane wave grid, and pseudopotentials developed by Goedecker and co-workers.[36] Isothermal-isobaric (NPT) MD simulations of both isomers were conducted. The species were properly embedded in the THF solvent model by determining, using atomic Pauling radii, the volume associated with their solvent accessible surface.[37] As the volume of THF is 2.96 times smaller compared to the volume of the 3-chloro-1-azaallylic anion, three THF molecules in the simulation cell were replaced by the 3-chloro-1-azaallylic species. An equilibration time of 2.5 ps has been respected to allow the solvent to accommodate to the presence of the solute and vice versa, followed by a 40 ps metadynamics run. Accurate metadynamics parameter values were determined from Gibbs free energy barrier predictions of the lithiated 3-chloro-1-azaallylic anion in the gas phase (using a supercell approach), including only one THF molecule to impose the limited freedom of the lithium cation. The set of parameter values $w=2.0$ kJ mol^{-1}, $s=0.33$ rad and $G=50$ fs (notation: see ref. [26]) yielded an energy barrier within 1.0 kJ mol^{-1} of the convergence limit. According to ref. [32] the estimated error using these parameters is $\varepsilon=6.1$ kJ mol^{-1}.

Lithiated 3-chloro-1-azaallylic anion 1: To a stirred solution of diisopropylamine (0.056 g, 0.55 mmol) in [D_8]THF (1 mL), *n*BuLi (0.22 mL, 0.55 mmol, 2.5 N in hexanes) was added slowly at 273 K. After 30 min of stirring at 273 K, the solution was evaporated in vacuo to dryness, after which, [D_8]THF (0.5 mL) was added and a solution of *N*-(2-chloro-1-phenylpropylidene)isopropylamine (0.11 g, 0.5 mmol) in [D_8]THF (0.5 mL) was dropped to the LDA solution at 273 K and stirring was continued for 1 h. Subsequently, the reaction mixture was allowed to reach room temperature during 15 min. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were taken from the prepared 3-chloro-1-azaallylic anion **1** at room temperature. ^{1}H NMR (300 MHz, [D_8]THF): $\delta=0.83$ (d, $J=6.33$ Hz, 6H; (CH_3)$_2$CH), 1.77 (s, 3H; CH_3), 2.96 (septet, $J=6.1$ Hz, 1H; (CH_3)$_2$C*H*), 7.08–7.14 (m, 3H; *o*-CH_{ar} and *p*-CH_{ar}), 7.18–7.24 ppm (m, 2H; *m*-CH_{ar}); ^{13}C NMR (75 MHz, [D_8]THF): $\delta=22.3$, 28.1, 48.6, 83.6, 125.9, 127.6, 130.0, 144.0, 155.0 ppm.

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Keywords: azaallylic anions · isomerization · metadynamics · NMR spectroscopy · solvent effects

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