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Stereochemistry of Metalated Aldimines. 1. An ab Initio Study of the Potential Energy Surfaces of Isolated Acetaldimine Anions, Their Monomeric Lithium and Sodium Ion Pairs, and Mechanistic Consequences[1]

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Equilibrium geometries and transition-state structures for *syn/anti* isomerization and CC rotation have been examined for the isomeric carbanions of acetaldimine and *N*-methylacetaldimine and for their ion pairs formed with Li and Na. Effects of the N-substituent and of the nature of the gegenion on the structures and topologies, relative stabilities, and activation energies are discussed and compared to oxyimine analogues. The π-conjugated *syn*- and *anti*-configured azaallyl anions, best considered as amide anions rather than carbanions, are minima and their thermodynamic *syn* preference accounts for the regiochemistry of reactions of the free ions. Ion-pair formation reverses the relative isomer stabilities; a preference for the *anti* configuration is found for the unsolvated monomeric ion pairs and also for the di- and trisolvated lithioacetaldimines. The most stable structures of the Li and Na ion pairs of the *syn*-metaloaldimines all involve η^1 N_σ coordination and in the *anti* isomers M^+ coordinates to the azaallylic system either in a π-fashion or exclusively to N. Racemizations of enantiomeric π-complexes are fast processes. The activation barriers for *syn/anti* isomerization of the ion pairs are smaller than in the free anions and all isomeric ion pairs are readily available for aggregate formation. The relative stabilities and the geometries of the *monomeric* ion pairs suggest that metalated imines are aggregated in ether solutions and, moreover, that the *monomeric ion pairs are not the reactive species* in reactions with electrophiles. Ion-pair catalysis of the reaction of the *syn*-configured ion pair is proposed as a possible mechanism for the kinetically controlled formation of the *syn* product. The mechanism responsible for the regioselective formation of a new bond to the α-carbon in the *syn* position of a metalated alkylimine thus appears to be entirely different from the mechanisms thought to be operative in similar reactions of metalated oxy- and aminoimine. In the case of the metalated imines, cooperative effects appear necessary to allow for the regioselectivity of the electrophile addition and the ion-pair dimer is discussed as the smallest conceivable reactive species.

Introduction

The regio- and stereoselective formation of a new carbon–carbon bond in the α-position to a carbonyl group is one of the fundamental reactions of modern synthetic organic chemistry.[2] The introduction of metalated N-substituted imines[3] has resolved many of the problems associated with the classical carbonyl chemistry[4] and metalated imines and other N derivatives of carbonyl compounds have since been applied for such carbon–carbon bond formations with great success.[5] One of the most remarkable characteristics of these metalorganic intermediates is the high regiospecificity of their formation; a remarkable preference for the *syn*-configured[6] metalated imine derivative is generally observed.[7–15] Moreover, the addition of electrophiles proceeds not only with *syn*-selectivity but also with stereoselectivity when imines derived from optically pure chiral amines are employed.[16–24]

For a full understanding of the stereochemical outcome of such reactions, accurate knowledge about the configuration of the metalated intermediates is indispensible. Many studies have thus focused on the study of the stereochemistry of the metalated azaallyl derivative and of the addition of such enolate equivalents with electrophilic reagents. The formation of the metalated imine may lead a priori to four isomers since hindered rotations around the CC and the CN bonds may result in pairs of E/Z isomers. An electrophilic reagent can in principle react with each of these isomers at carbon or at nitrogen. The addition of the electrophile occurs in general at carbon; only protonations occur regiospecifically at nitrogen[17] and acylations result in competition between C- and N-acylation.[7]

The first evidence for the preferential *syn* reaction was reported by Fraser et al.[8] ^{1}H NMR in DMSO showed 98% of the *syn*-deuterated product. Monitoring the methylation of several lithiated *N*-isopropyl imines of cyclic ke-

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tones by ^{13}C NMR-spectroscopy[9] showed the alkylation to occur exclusively (99%) at the *syn* α-carbon (*Z* product) under kinetic conditions and suggested an advantage of at least 1.8 kcal/mol for the *syn* reaction path. When configurationally rigid imines were allowed to react under the same conditions, the methylation proceeded *syn* selectively *and* stereoselectively and *syn*-axial methylated products were obtained. Metalated aldimines behave similarly. Metalation and methylation of the α-methylphenylethylamine derivative of butanal gave 96% of the *Z* product, although the neutral *E* imine is thermodynamically preferred. The *syn* preference energy of at least 1.2 kcal/mol for the formation of the *Z* product and the thermodynamic preference of 3.1 kcal/mol of the neutral *E* imine give a value of 4.3 kcal/mol for the factor that stabilizes the *syn*-configured transition state.[10] In contrast to the exocyclic counterparts, endocyclic ketimines have been found to be alkylated preferentially at the *anti* α-carbon.[10] Ab initio calculations of the isomeric anions[11,12] of acetaldimine and *N*-methylacetaldimine at the 4-31G level gave *syn*-preference energies of 4.7 and 6.2 kcal/mol, respectively. Houk et al.[11] attributed the *syn* preference primarily to the destabilization of the *anti* anion caused by repulsion between the N_σ lone pair and the CH_2 group. The preference of endocyclic ketimines for the formation of the *anti*-configured intermediate has been assigned to ring strain; ring strain prevents the NCC angle from assuming a value typical of acyclic imine anions (ca. 130°) and thus destabilizes the *syn* isomer. Acidity measurements of several aldimines and ketimines in THF provide further support for the experimental and theoretical results.[13] The acidity data indicate the *syn*-preference energy for the formation of the lithiated imines to be at least 4 kcal/mol for acyclic and exocyclic imines and the pK_a data also account for the *anti* preference of endocyclic ketimines. The selective formation of the *syn* intermediate may or may not involve site-specific deprotonation. In the case of an N-substituted acetaldimine, for example, the *syn*-configured intermediate can in principle result from (i) nonspecific hydrogen abstraction followed by rapid *syn/anti* isomerization, (ii) site-selective deprotonation at the *syn* α-carbon, or (iii) selective deprotonation at the *anti* α-carbon followed by rapid *syn/anti* equilibration of the metalated intermediate.

Metalation of α-substituted imines results preferentially in the formation of the CC *E* isomer under kinetic conditions. Desilylation of *N*-silyl-*N*-methyl enamines with methyllithium in THF results in the CC *E*-configured lithiated imines.[16] Knorr et al.[17] have shown that metalation of *N*-phenylphenylethylketimine with LDA in THF at −70 °C results in a 3:1 mixture of the *E* and *Z* CC isomers of the lithiated imine. The isomer ratio is not changed upon heating up to 60 °C. However, thermodynamic equilibrium (*Z* isomer favored) can be achieved when a catalytic amount of the imine (a weak acid) is added.[17] Bergbreiter et al.[18] conducted similar studies with aldimines simultaneously. As with the ketimines a preference for the *E* isomer (here 100%) was observed. Interestingly, it was found that hexamethylphosphoric triamide (HMPT) affects the CC *E*/*Z* ratio; metalation of *N*-cyclohexylpropanaldimine in the presence of HMPT gives a mixture in which the *Z* isomer (56%) predominates. Moreover, thermodynamic equilibrium between the CC isomers (82% *E*) in only obtained at 27 °C if HMPT is present. An activation barrier of 22.6 kcal/mol has been measured for the CC isomerization. For the CH_2 rotation of *N*-alkylacetaldimine an activation barrier of about 17 kcal/mol has also been reported.[18] An elegant illustration of the synthetic usefulness of the preferential formation of thermodynamically unfavored CC *E* isomer under kinetic conditions and its equilibration to the more stable *Z* isomer is given by the work of Meyers et al.[19]

Many aspects concerning the configuration of metalated imines are thus well established. Yet, the structure of the intermediates and the reasons for the preferential formation of CC *E*/CN *syn*-configured intermediate are not fully understood. Fraser et al have argued that the formation of the *syn*-configured intermediate reflects an intrinsic property of the imine carbanion[11,12] and chelation was considered to be unimportant.[8,10] Many other workers have considered the role of the metal as crucial[16-21,23] and discussed either π-coordinated azaallyl structures or N-metalated vinylamides in reaction mechanisms.

In this paper we report the results of an ab initio investigation of the imine carbanions and their metal derivatives. Monomeric species have generally been discussed for such species and monomers are considered here. The role of aggregation in solution is still a subject of controversy. The first X-ray structure determination of a lithiated Schiff base, *N*-(2,2-dimethyl-1-methylenepropyl)benzenamine, showed the existence of dimeric aggregates in the crystal.[25] Studies by Wanat and Collum[26] on the structure of the closely related metalated hydrazones demonstrate that aggregation in the solid state does not necessarily carry over to solutions. Also, recent theoretical and experimental studies in our group provide evidence that monomers may still be the reactive species even if ion-pair aggregation is important.[27] The potential energy surfaces of the carbanions of the parent acetaldimine and of its *N*-methyl analogue and of their monomeric lithium and sodium derivatives were investigated. Equilibrium geometries and transition-state structures for *syn/anti* isomerization and CH_2 rotation are reported. Relative isomer stabilities and activation barriers for their isomerizations are reported and the effects of ion-pair formation on these values are analyzed. The racemization pathways for chiral ion pairs are considered as well. The structural and energetic effects of the nature of the cation and of the N-substituent are discussed and comparisons are made with the corresponding data for metalated oxime carbanions.[28,29] The effects of primary solvation were studied for the di- and trisolvated lithioacetaldimines. The results presented suggest that colligative effects need to be invoked to explain the stereochemistry of reactions of metalated imines with electrophiles.

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Table I. Energies and Vibrational Zero-Point Energies of Stationary Points of the Isolated Anions of Acetaldimines and *N*-Methylacetaldimine and of Their Ion Pairs Formed with Lithium and Sodium

molecule[a]				3-21+G[b,c]	6-31+G*[b,d]	ZPE[e]	NIMAG[f]
				$HNCHCH_2^-$			
1	*syn*	C_s	π	131.723 417	132.448 701	36.26	0
2	*anti*	C_s	π	131.717 870	132.444 106	36.04	0
3	*syn*	C_s		131.681 250	132.412 272	35.08	1
4	*syn*	C_s		131.676 962	132.406 899	35.07	1
5	*anti*	C_s		131.661 736	132.396 769	34.34	1
6	*anti*	C_s		131.667 065	132.399 202	34.84	1
7		C_1		131.693 282	132.416 277	34.83	1
8		C_s		131.671 809	132.388 329	34.08	2
				$HNCHCH_2^-Li^+$			
9	*anti*	C_1	π	139.182 839	139.949 469	39.02	0
10	*anti*	C_s	π	139.179 266	139.942 210	38.61	0[g]
11	*anti*	C_1		139.179 264	139.943 057	38.57	1[g]
12	*anti*	C_s		139.160 853	139.932 113	38.11	1
13	*anti*	C_s		139.118 542	139.986 435	37.67	1
14	*syn*	C_s	π	139.178 539	139.941 092	39.09	0
15	*syn*	C_s		139.122 983	139.899 753	37.82	1
16				139.165 151	139.926 163	38.16	1
				$HNCHCH_2^-Na^+$			
17	*anti*	C_s	π	292.639 157	294.323 948	38.51	0
18	*syn*	C_s	π	292.634 794	294.318 526	38.47	0
				$MeNCHCH_2^-$			
19	*syn*	C_s	π	170.533 278	171.478 240	55.23	0
20	*anti*	C_s	π	170.523 687	171.470 786	54.46	0
21	*anti*	C_s	π	170.522 986	171.469 871	54.27	1
22				170.497 682	171.442 483	56.05	1
				$MeNCHCH_2^-Li^+$			
23	*anti*	C_1	π	177.989 252	178.975 210	57.66	0
24	*anti*	C_s	π	177.982 215	178.964 398	56.98	1
25	*anti*	C_s	π	177.981 087	178.963 675	56.74	2
26	*syn*	C_s	π	177.984 700	178.965 293	58.19	0
27	*syn*	C_1	π	177.966 945	178.959 501	57.81	0
28		C_1		177.967 502	178.947 305	57.03	1
				$MeNCHCH_2^-Na^+$			
29	*anti*	C_1	π	331.449 584	333.349 170	57.12	0
30	*anti*	C_s	π	331.448 256	333.345 109	57.06	1
31	*anti*	C_s	π	331.446 267	333.344 797	56.76	2
32	*syn*	C_s	π	331.446 620	333.341 463	58.16	0
				$HNCHCH_2^-Li^+\cdot 2H_2O$[h]			
33	*anti*	C_s		290.423 243	292.027 439		
34	*syn*	C_s		290.425 196	292.026 374		
				$HNCHCH_2^-Li^+\cdot 3H_2O$[h]			
35	*anti*	C_s		366.039 321	368.056 077		
36	*syn*	C_s		366.036 992	368.053 134		

[a] Pseudo-π- or π-conjugation in the carbanion is indicated by "π". [b] E in atomic units. [c] Sets of single sp-diffuse functions were added to the atoms of the azaallylic skeleton. [d] Single-point calculations based on the 3-21+G optimized structures. No d functions were used for the description of the cations at the 6-31+G*/3-21+G level. [e] Calculated analytically at 3-21+G and unscaled. [f] Number of imaginary frequencies. [g] See text. [h] Solvated systems optimized at 3-21G and single-point energy computations at the 6-31+G*/3-21G level.

Methods

Restricted Hartree–Fock calculations were performed with the program GAUSSIAN88 and earlier versions.[30] Stationary structures were optimized using Schlegel's gradient technique[31] under the constraints of the symmetry point group specified. The optimizations of stationary structures of the carbanions were carried out with a slightly modified version of the 3-21+G basis set;[32] the 3-21G basis set[33] was augmented by shells of single diffuse functions on all heavy centers of the azaallyl system. In the calculations of the ion pairs the metal cations were described by the 3-21G basis set while the associated anions were described with the same basis that was used for the isolated anions. This choice of basis set, denoted 3-21+G despite the modest modification, provides a more balanced functional description of the associated cations.[34] Reliable energies were calculated with a modestly modified version of the 6-31+G* basis set.[32,35] Augmentation by diffuse functions was done as in the case of the smaller basis set. No d functions were used for the description of the metals. These functions are not necessary for the proper description of the metal cations but would only serve to increase the number of empty orbitals at the metal atoms and lead to increased basis set superposition error.[34] Harmonic vibrational frequencies[36] were calculated at the level of optimization to characterize stationary points as minima or saddle points and to obtain vibrational zero-point energies. The vibrational zero-point energy corrections to relative energies were scaled (factor 0.9) to account for their general overestimation at this theoretical level.[37] Calculations were carried out in part on various Vax workstations,

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Table II. Relative Energies[a–c]

molecules		3-21+G		6-31+G*	
A	B	SCF	SCF+ZPC	SCF	SCF+ZPC
1	**3**	26.47	26.41	22.86	22.80
1	**4**	29.15	29.08	26.23	26.16
1	**7**	18.91	17.63	20.35	19.07
1	**8**	32.38	30.42	37.88	35.92
2	**5**	35.22	33.68	29.70	28.16
2	**6**	31.88	30.80	28.20	27.12
2	**7**	15.43	14.34	17.46	16.37
2	**8**	28.90	27.14	35.00	33.24
9	**10**	2.24	1.87	4.56	4.15
9	**11**	2.24	1.83	4.02	3.61
9	**12**	13.80	12.98	10.89	10.07
9	**13**	40.35	39.13	33.28	32.06
9	**16**	11.10	10.33	14.62	13.83
14	**15**	34.86	33.72	25.94	24.80
14	**16**	8.40	7.56	9.37	8.53
19	**22**	22.34	21.05	22.44	21.15
20	**22**	16.32	15.99	17.76	17.43
20	**21**	0.44	0.27	0.57	0.40
24	**25**	1.30	1.20	0.46	0.95
23	**24**	4.42	3.80	6.78	6.17
23	**25**	5.12	5.00	7.24	7.12
23	**28**	13.65	13.08	17.51	16.94
26	**27**	11.14	10.80	5.52	15.18
26	**28**	10.79	9.99	11.23	10.46
29	**30**	0.83	0.78	2.55	2.50
29	**31**	2.08	1.76	2.74	2.42
30	**31**	1.25	0.98	0.20	0.07

[a] Values specify the energy by which A is more stable than B in kcal/mol. [b] Based on the 3-21+G optimized structures. [c] Vibrational zero-point energies are scaled (factor 0.9).

Table III. *syn*-Preference Energies[a–c]

molecules		3-21+G		6-31+G*	
A	B	SCF	SCF+ZPC	SCF	SCF+ZPC
1	**2**	3.48	3.29	2.88	2.69
14	**9**	−2.70	−2.76	−5.26	−5.32
18	**17**	−2.74	−2.70	−3.40	−3.36
19	**20**	6.02	5.06	4.68	3.72
26	**23**	−2.86	−1.68	−6.22	−5.04
32	**29**	−1.86	−2.80	−4.84	−5.78
34	**33**	1.23		−0.67	
36	**35**	−1.46		−1.85	

[a] Values give the energy by which the *syn*-configured isomer A is more stable than the *anti*-configured isomer in kcal/mol. [b] Based on the 3-21+G-optimized structures in general and based on the 3-21G-optimized structures for the solvated systems. [c] Vibrational zero-point energies are scaled (factor 0.9).

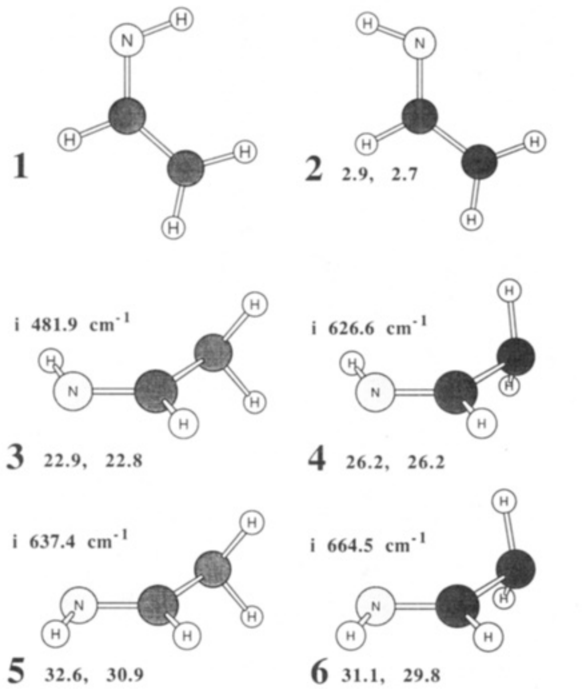


Figure 1. Planar structures of the *syn*- and the *anti*-configured anions of acetaldimine, **1** and **2**, are minima. Structures **3–6** are the transition-state structures (C_s) for CC rotation. Here and in the following figures, relative energies are given that were calculated at 6-31+G*/3-21+G without and with inclusion of the vibrational zero-point energy corrections (3-21+G) in kcal/mol. For the *anti* isomers **5** and **6** the activation energies E_A for CC rotation are given at the same level.

the Vax-8800 at the UCB Computer Center, the Cray II at the San Diego Supercomputer Center, and on the IBM 3090 mainframe of the UMC Campus Computer Center.

Results and Discussion

Energies and vibrational zero-point energy corrections for the anions and the ion pairs of acetaldimine and *N*-methylacetaldimine are listed in Table I. Relative energies and *syn* preference energies are summarized in Tables II and III, respectively.

Potential Energy Surface of Acetaldimine Carbanion. Configurational Preference. The planar structures of the *syn* anion, **1**, and of the *anti* anion, **2**, are minima and molecular-model-type drawings of these anions are shown in Figure 1. Structural data of the isolated anions are listed in Tables IV and V. The geometries of

Table IV. Structures of the Acetaldimine Anions 1–8[a–d]

	syn			*anti*			*syn* to *anti*	
parameter	**1**	**3**	**4**	**2**	**5**	**6**	**7**	**8**
NH	1.019	1.018	1.018	1.015	1.020	1.021	1.018	0.975
NC	1.338	1.280	1.287	1.343	1.285	1.288	1.396	1.294
$C\underline{C}$	1.382	1.501	1.505	1.373	1.488	1.497	1.347	1.386
$\underline{C}H_s$	1.079		1.094	1.076		1.095	1.077	1.077
$\underline{C}H_a$	1.077	1.097		1.077	1.097		1.080	1.078
CH	1.084	1.092	1.084	1.095	1.109	1.095	1.099	1.104
HNC	111.6	109.8	111.5	111.4	112.0	112.5	113.1	181.6[e]
$NC\underline{C}$	132.4	126.4	129.9	128.2	126.8	127.9	128.6	130.7
$H_s\underline{C}C$	121.5		111.6	121.1		109.8	121.0	121.6
$H_a\underline{C}C$	120.7	110.1		120.6	109.8		121.2	119.8
HCN	112.6	113.1	112.8	117.9	115.1	116.3	117.2	117.4
$H_s\underline{C}CN$	0.0		62.1	0.0		59.4	−3.5	0.0
$H_a\underline{C}CN$	180.0	120.5		180.0	120.4		174.1	180.0

[a] **1–6** and **8** are C_s-symmetric and **7** is chiral. In angstroms and degrees. [b] The CH_2 carbon is underlined. H_s and the CN bond are cisoid. [c] The C lone pair and the CN bond are trans in **4** and **6**. [d] See supplementary material for further structural data of **7**. [e] The H(N) and $\underline{C}$ are trans with respect to the CN bond.

Table V. Structures of the Anions of *N*-Methylacetaldimine 19–22[a–c]

parameter	19	20	21	22
NC′	1.470	1.469	1.476	1.478
NC	1.331	1.326	1.333	1.389
$\mathrm{C\underline{C}}$	1.383	1.378	1.374	1.347
$\mathrm{\underline{C}H_s}$	1.075	1.076	1.076	1.077
$\mathrm{\underline{C}H_a}$	1.077	1.077	1.077	1.079
CH	1.083	1.098	1.098	1.101
$\mathrm{C'\underline{H}}$	1.085	1.100	1.085	1.098
C′H′	1.096	1.090	1.098	1.104
C′H″				1.086
CNC′	114.8	116.6	114.5	113.3
$\mathrm{NC\underline{C}}$	131.6	129.1	128.2	128.5
$\mathrm{H_sC\underline{C}}$	123.0	121.3	121.1	121.1
$\mathrm{H_aC\underline{C}}$	119.9	120.3	120.5	121.4
HCN	112.9	116.8	117.2	117.0
$\mathrm{\underline{H}C'N}$	108.5	112.9	108.4	114.0
H′C′N	112.7	111.3	113.5	114.0
H″C′N				108.1
$\mathrm{H_s\underline{C}CN}$	0.0	0.0	0.0	−0.7
$\mathrm{H_a\underline{C}CN}$	180.0	180.0	180.0	177.1
$\mathrm{\underline{H}C'NC}$	180.0	0.0	180.0	−54.0
$\mathrm{H'C'N\underline{H}}$	119.8	120.9	118.9	121.9
$\mathrm{H''C'N\underline{H}}$				−119.4

[a] **19–21** are C_s-symmetric and **22** is asymmetric. In angstroms and degrees. [b] The CH_2 carbon and the in-plane H are underlined. Hs and the CN bond are cisoid. C′ denotes the CH_3 carbon and the methyl hydrogens are *H*, H′ and H″. $\underline{\mathrm{H}}$ lies in the molecular plane in **19–21**. [c] See supplementary material for further structural data of **22**.

1 and **2** are in good agreement with the 4-31G structures reported earlier by Houk et al.[11] but the *syn* preference energy is found to be smaller. At 6-31+G*/3-21+G the *syn* isomer **1** is thermodynamically favored by 2.9 kcal/mol. The inclusion of vibrational zero-point energy corrections results in a slightly reduced *syn* preference energy of 2.7 kcal/mol.

CC Rotational Barriers. Four C_s-symmetric stationary points with pyramidal CH_2 groups were optimized (Figure 1). In the *syn*(*anti*-)configured anion **3** (**5**) the C lone pair is oriented toward N and in **4** (**6**) it extends in the opposite direction. The calculated vibrational frequencies identify all of these structures as transition-state structures for CH_2 rotation. The activation barriers for CH_2 rotation in **1** via **3** and **4** are 22.8 and 26.2 kcal/mol, respectively, at the highest level. The activation barriers for the CH_2 rotation in the *anti* isomer via **5** and **6** are 28.2 and 27.1 kcal/mol, respectively, at the same level. The lowest energy pathway for rotation around the CC bond in the *syn* isomer **1** is thus about 6 kcal/mol above the barrier measured for *N*-alkylacetaldimine.[18] The activation barrier of acetaldimine anion presumably represents a lower limit for the activation energy required for CH_2 rotation in N-alkylated acetaldimines for steric reasons.

***syn*/*anti* Isomerization.** The *syn*/*anti* isomerization can in principle involve two distinct modes of the H(N) movement depending on whether the dihedral angle HNCC or the angle HNC becomes the principal reaction coordinate. It is found that the *syn*/*anti* isomerization proceeds via rotation of the H(N) atom around the CN axis with only small changes of the HNC angle. The transition-state structure **7** is shown in Figure 2. The activation energies for the processes **1** to **2** and **2** to **1** are 19.1 and 16.4 kcal/mol, respectively, at the highest level. The C_s-symmetric stationary structure **8** is substantially higher in energy than **7** and structure **8** is not a transition state but a second-order saddle point (i1229.3 and i731.5 cm^{-1}).

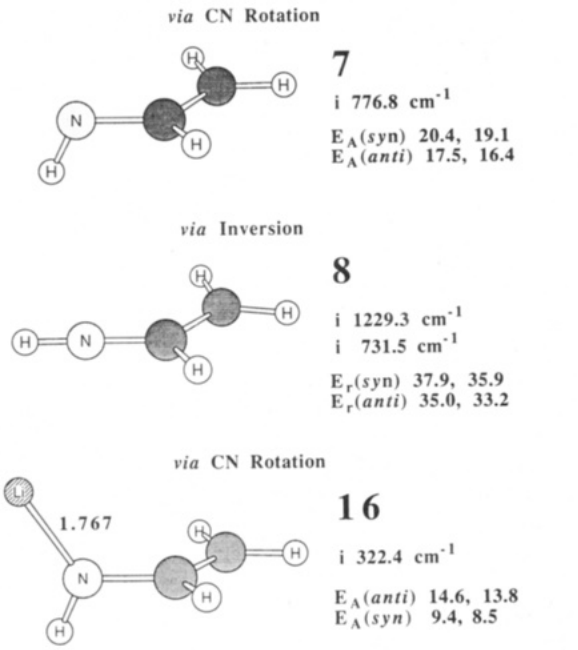
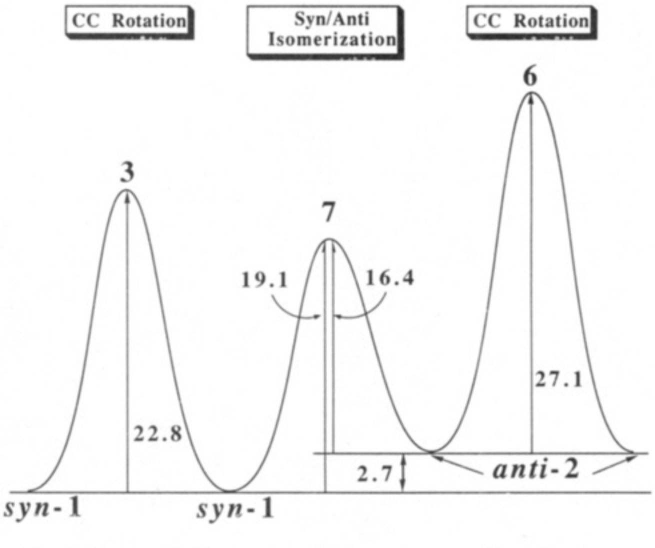


Figure 2. *syn*/*anti* isomerization of the acetaldimine anion involves a CN rotation mechanism and proceeds via the transition-state structure **7**. Isomerization via inversion at N does not occur; the structure **8** is a second-order saddle point. $E_A(syn)$ and $E_A(anti)$ give the energies of the saddle points with respect to the *syn*- and the *anti*-configured anions **1** and **2**, respectively. Here and in the following figures imaginary frequencies are given for structures that are saddle points. **16** is the transition-state structure for *syn*/*anti* isomerization of the lithium ion pair of acetaldimine. $E_A(syn)$ and $E_A(anti)$ give the relative energies with respect to the ion pairs *syn*-**14** and *anti*-**9**, respectively.

Scheme I



In Scheme I, the potential energy surface is drawn schematically but to scale for the isomeric anions, their interconversion, and for the CC rotations. The CN *syn*/*anti* isomerization of acetaldimine anion is a more facile process than the rotation of the CH_2 group. The difference in the activation energies of the two processes simply reflects the different stabilities of N- and C-centered anions. We have recently shown that the anions **1** and **2** are best described as amides rather than carbanions.[38] The CC rotation requires strong internal charge transfer from N to the CH_2 carbon (*carbanion* transition

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[38] Glaser, R. *J. Comput. Chem.* **1989**, *10*, 118.

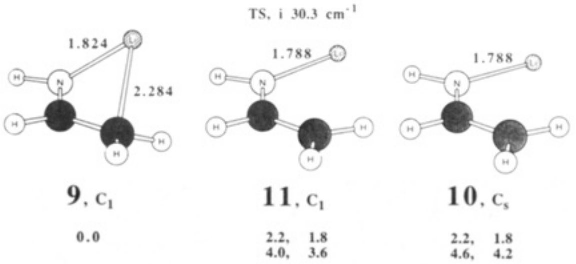


Figure 3. Structure of the global minimum of the lithium ion pair of the *anti*-configured acetaldimine **9**. **10** corresponds to a minimum on the 3-21+G surface and **11** is the transition state between **9** and **10**. Relative energies are given at the 3-21+G level (without and with inclusion of vibrational zero-point energy corrections; upper values) and at the 6-31+G*/3-21+G level. The higher level calculations show **10** to be the de facto transition-state structure for racemization.

Table VI. Selected Bond Distances Involving the Cation M

molecule		M	M–C_C	M–C_N	M–N
9	*anti*	Li	2.283	2.218	1.824
10	*anti*	Li	3.088	2.743	1.788
11	*anti*	Li	3.059	2.725	1.788
12	*anti*	Li	2.058	2.305	1.942
13	*anti*	Li	2.021	3.093	4.297
14	*syn*	Li	4.140	2.868	1.778
15	*syn*	Li	2.024	3.049	4.285
16		Li	3.691	2.818	1.767
17	*anti*	Na	2.797	2.696	2.028
18	*syn*	Na	4.043	3.144	2.014
23	*anti*	Li	2.243	2.184	1.825
24	*anti*	Li	2.946	2.652	1.786
25	*anti*	Li	2.775	2.557	1.795
26	*syn*	Li	4.111	2.820	1.775
27	*syn*	Li	2.406	2.098	1.937
28		Li	3.712	2.778	1.761
29	*anti*	Na	2.562	2.518	2.031
30	*anti*	Na	2.673	2.597	2.018
31	*anti*	Na	2.629	2.569	2.024
32	*syn*	Na	4.111	2.769	2.009
33	*anti*	Li	3.172	2.800	1.848
34	*syn*	Li	4.179	2.888	1.838
35	*anti*	Li	3.152	2.814	1.933
36	*syn*	Li	4.212	2.898	1.906

[a] In angstroms.

state) whereas the *syn*/*anti* isomerization requires primarily reorganization of the electron density at N (*amide* transition state) and only minor additional electron transfer toward nitrogen. These electronic changes along the isomerization paths are reflected in the geometries of the anions. Internal charge transfer toward the CH_2 carbon leads to short CN bonds (1.28–1.29 Å) and CC single bonds (1.49–1.50 Å) in the carbanions **3**–**6**. In contrast, the bond lengths in **7** are changed less and in the opposite direction (Table IV).

Potential Energy Surfaces of the Lithium and Sodium Ion Pairs of Acetaldimine Carbanion. *anti*-Configured Lithium Ion Pairs. The global minimum on the potential energy surface of the lithium ion pair of acetaldimine does *not* have the *syn* configuration. Instead, the anti-configured lithium ion pair **9** shown in Figure 3 is the global minimum. In the chiral structure **9**, the lithium engages in an η^3 face coordination. Major structural parameters of the anion within the ion pairs and selected distances involving the cation are listed in Tables VI and VII. The pseudo-π-system within the ligand persists in the ion pair and only a slight pyramidalization is found for the CH_2 group. Note that the NCC angle is reduced significantly compared to the isolated anion.

The structure **10** was optimized to determine the activation energy for racemization of **9** via a planar, η^1-N_σ-coordinated transition state. However, the vibrational frequencies identify the *N*-lithiovinylamine **10** as a local minimum only 1.8 kcal/mol less stable than **9** at 3-21+G and including vibrational zero-point energy corrections. The transition-state structure **11** for the interconversion between **9** and **10** is essentially isoenergetic with **10**; the energy at 3-21+G is 2.24 kcal/mol for both structures and the inclusion of the vibrational zero-point energy favors **10** by only 0.03 kcal/mol. The lowest vibrational frequency of **10** is 30.6 cm^{-1} and the imaginary frequency of **11** is i30.3 cm^{-1}. Obviously, **10** corresponds to an extremely shallow minimum on the 3-21+G energy surface. At the 6-31+G*/3-21+G level **10** is in fact 0.6 kcal/mol *higher* in energy than **11**. **10** thus appears to be the de facto transition-state structure for the facile racemization of the chiral ion pair **9** and the associated activation barrier is 4.2 kcal/mol at the highest level.

Table VII. Major Bond Lengths and Angles of the Anions in the Ion Pairs of Acetaldimine 9–18 and *N*-Methylacetaldimine 23–30 and in the Solvated Ion Pairs 33–36[a,b]

molecule[c]	E–N	N–C	C–$\underline{C}$	E–N–C	N–C–$\underline{C}$
9	1.004	1.357	1.372	115.7	122.1
10	1.006	1.381	1.345	112.2	126.2
11	1.006	1.381	1.345	112.4	126.1
12	1.009	1.288	1.506	117.4	118.5
13	1.015	1.272	1.514	114.7	123.7
14	1.013	1.386	1.340	110.7	129.3
15	1.017	1.272	1.526	114.0	127.8
16	1.012	1.430	1.329	111.1	126.3
17	1.008	1.366	1.357	111.6	126.9
18	1.017	1.377	1.344	108.7	128.7
23	1.468	1.343	1.379	118.5	122.7
24	1.476	1.372	1.348	114.8	126.7
25	1.472	1.363	1.354	117.3	126.5
26	1.476	1.375	1.345	114.3	129.8
27	1.482	1.360	1.372	115.2	127.8
28	1.488	1.423	1.330	112.6	126.4
29	1.473	1.351	1.370	114.4	126.0
30	1.475	1.357	1.363	113.8	128.3
31	1.473	1.350	1.368	116.2	128.6
32	1.468	1.368	1.348	113.5	129.8
33	1.008	1.367	1.344	111.3	127.9
34	1.015	1.370	1.341	110.4	130.9
35	1.010	1.348	1.361	111.3	129.0
36	1.016	1.360	1.347	111.0	129.0

[a] In angstroems and degrees. [b] See supplementary material for further structural data. [c] E represents H in the case of acetaldimine and CH_3 for *N*-methylactaldimine derivatives. The deprotonated carbon atom is underlined.

The structures **12** and **13** shown in Figure 4 are transition states for the racemization of **9** with concomitant rotation of the CH_2 group. The cation bridges in a 1,3-(C,N)-σ-fashion in **12** and the activation barrier to CC rotation of the ion pair is found to be 10.1 kcal/mol at the highest level. The transition state **13** involves only a single coordination between the cation and the CH_2 carbon and makes this pathway uncompetitive (E_A = 32.1 kcal/mol). The barrier to CC rotation in the *anti*-configured acetaldimine carbanion is thus reduced by 17.0 kcal/mol in the ion pair compared to the isolated anion. In Scheme II, the potential energy surface of the lithioacetaldimine is summarized schematically in the same fashion and with the same scale as has been done for the anion in Scheme I. Note that in a coordinating solvent such as THF the difference between **12** and **13** is expected to be reduced by the additional solvent coordination possible in **13** but this effect is unlikely to change the qualitative results.

***syn*-Configured Lithium Ion Pairs.** The lithium engages in a single N_σ coordination in the most stable ion-pair structure with the *syn* anion of acetaldimine, C_s-**14**

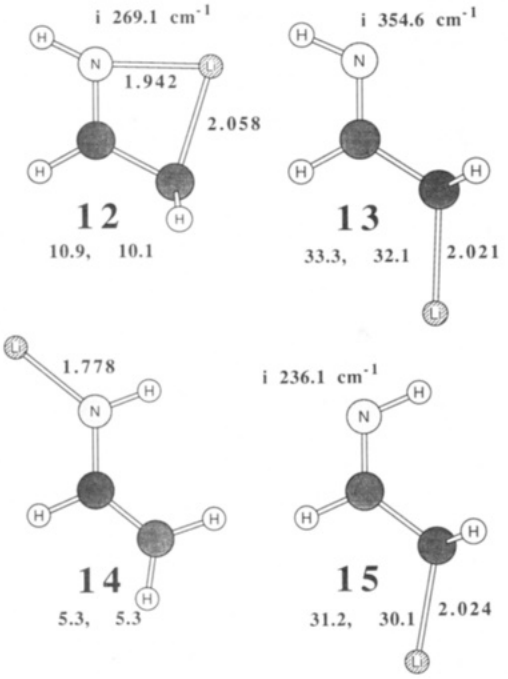
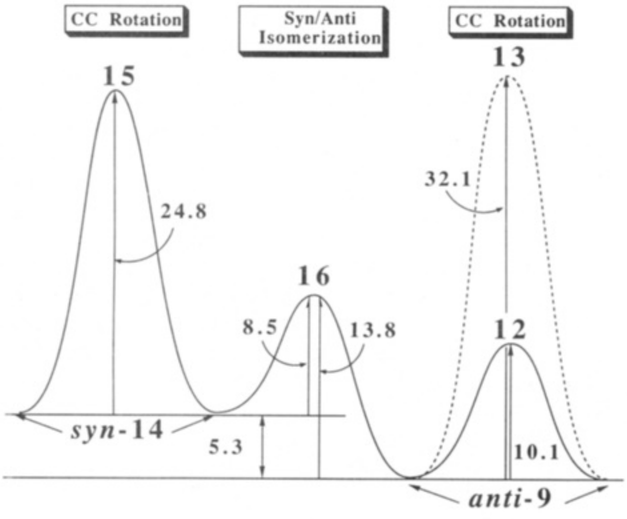


Figure 4. 12 and 13 are the transition-state structures for CC rotation in the *anti*-configured lithium ion pair. 14 is the only minimum of the lithium ion pair of the *syn*-configured acetaldimine and 15 is a transition-state structure for CC rotation. Relative energies are given with respect to the most stable lithium ion pair of acetaldimine, **9**, and the activation barriers are given with respect to 14.

Scheme II



(Figure 4). **14** is 5.3 kcal/mol less stable than *anti*-**9**. A π-complex-type structure for the *syn*-configured ion pair apparently does not correspond to a local minimum; no such minimum was found in a careful scan of the potential energy surface.

The CC rotation in the *syn*-configured lithium ion pair appears to be energetically disfavored compared to a sequence of steps involving *syn*/*anti* isomerization of the ion pair (vide infra) and CC rotation of the *anti*-configured ion pair. The only transition state for CC rotation without concomitant *syn*/*anti* isomerization involves single coordination of Li to the pyramidalized carbon as in C_s-**15** (Figure 4). However, **15** is 24.8 kcal/mol less stable than **14** and the activation energy for the process **14** via **15** to **14** is thus 11.0 kcal/mol higher than the highest activation barrier (13.8 kcal/mol activation for **9** to **16**) along the path **14** via **16** to **9**, CC rotation via **12**, and **9** via **16** to **14**.

Further Discussion. The results concerning the minimum structures of the lithium ion pairs are in disagreement with the prior 4-31G calculations.[11] Houk et al. reported the energies of a π-complex and of a η^1-N_σ-coordinated *anti*-configured structure. It was not reported whether the η^1-N_σ-coordinated structure represents a local minimum or a transition state. In any case, the energy difference between the two stationary structures was reported to be 16.6 kcal/mol, much larger than the value of 4.2 kcal/mol found in the present study. Also, at 4-31G a *syn*-configured π-complex was reported as a local minimum 12.6 kcal/mol higher in energy than the η^1-N_σ-coordinated *syn*-configured ion pair; such a minimum does not exist on the 3-21+G surface. Furthermore, a value of 16.1 kcal/mol was reported for the preference of the *anti*-configured ion pair whereas our calculations result in the much lower value of 5.3 kcal/mol. The disagreement may be caused by the different susceptibilities of the basis sets to superposition errors on structures and energies. At the 4-31G level the empty orbitals of the L shell of the cation are presumably used to a significant extent to improve the description of the electron density of the anion. At the 3-21+G and 6-31+G*/3-21+G levels superposition should be less important. The improvement in the description of the anion by the triply split valence shell should counteract superposition effectively and provide correct structures of the ion pairs and, especially at the 6-31+G*/3-21+G level, provide better relative energies. The additional stabilization of the anion by a superposition mechanism would be larger for π-complexes than for single-coordinated ion pairs. It is possible that this extra stabilization causes the local minimum for the *syn*-configured π-complex to exist artificially on the 4-31G surface. Such extra stabilization would also account for the overestimation of the 4-31G energy gap between the two topologically different stationary structures of the *anti*-configured ion pairs.

***syn*/*anti* Isomerization in the Lithium Ion Pair.** The transition-state structure for the *syn*/*anti* conversion of the lithium ion pair of acetaldimine, **16**, is shown in Figure 2. The CN bond in **16** is significantly lengthened compared to the minima **9** and **14** while the opposite is true for the CC bond. Similar structural effects have been found for the transition state for *syn*/*anti* conversion of the isolated anions. In both cases the isomerization is accompanied by charge accumulation at N in the transition state. Since complexation of N by Li facilitates such charge accumulation it was to be expected that the *syn*/*anti* isomerization be facilitated under ion-pair conditions. Comparison of Schemes I and II nicely illustrates the point. The activation energies required for the processes **14** to **9** and **9** to **14** are 8.5 and 13.8 kcal/mol, respectively.

Sodium Ion Pairs. The potential energy surface of the sodium derivative of acetaldimine was searched for minima only. As with the lithium ion pair, the global minimum has the *anti* configuration. In contrast to the lithium case, however, Na coordinates solely to the N_σ lone pair (Figure 5). A structure in which sodium π-coordinates has been searched for but such a stationary structure could not be found.[39] The *anti*-configured sodium ion pair is thus planar whereas the corresponding lithium derivative exists as a racemic mixture of rapidly equilibrating enantiomers. No topological differences are found between the *syn*-configured ion pairs of lithium and sodium. In the *syn*-configured sodium ion pair **18** (Figure 5), Na coordinates

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[39] Schleyer, P. v. R.; Clark, T.; Kos, A. J.; Spitznagel, G. W.; Rohde, C.; Arad, D.; Houk, K. N.; Rondan, N. G. *J. Am. Chem. Soc.* **1984**, *106*, 6467.

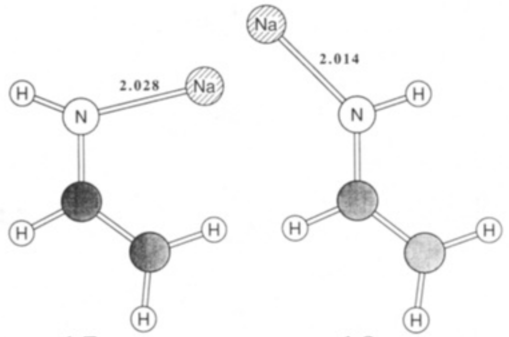


Figure 5. Structures of the sodium ion pairs formed with the *anti*- and the *syn*-configured acetaldimine anion, **17** and **18**.

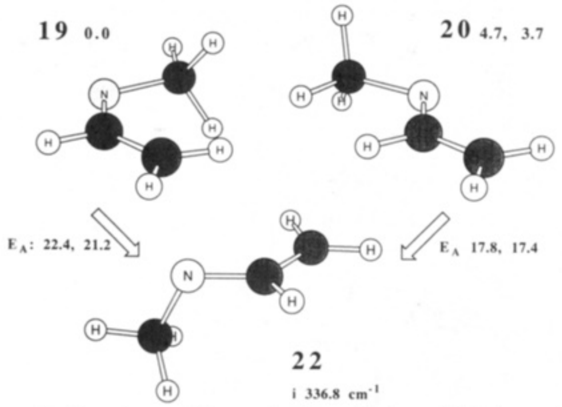
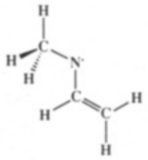


Figure 6. Structures of isomeric *N*-methylacetaldimine anions **19** (*syn*) and **20** (*anti*) and the transition-state structure for the interconversion, **22**.

solely to nitrogen and no minimum could be found for a π-complex-type structure. The *anti*-configured ion pair **17** is thermodynamically favored by 3.4 kcal/mol.

Effects of *N*-Methyl Substitution. Effects on Structures, *syn* Preference Energies, and the *syn*/*anti* Isomerization of the Anion. The minima (C_s) of the *syn* and *anti* anions of *N*-methylacetaldimine are shown in Figure 6. In the equilibrium structure of the *syn*-configured anion **19** the N_σ lone pair and the in-plane methyl hydrogens are eclipsed in order to avoid steric interactions between the CH_3 and the CH_2 groups. Steric interactions of this sort are less important in the *anti* isomer. In the optimized minimum structure **20** the N_σ lone pair and the methyl hydrogens are staggered and the transition-state structure **21** for the almost free rotation of the methyl group is only 0.4 kcal/mol higher in energy. The H/CH_3 exchange has but minor effects on the structures of the anions. Only the ENC angle (E = H, CH_3) is affected significantly. The increase of this angle (*syn*: 3.6°, *anti*: 5.2°) presumably serves to reduce steric repulsion. N-Methyl substitution causes the *syn*-preference energy of the anions to be increased; at the highest level **19** is favored over **20** by 3.7 kcal/mol while the *syn*-preference energy for the unsubstituted anions is 2.7 kcal/mol. As with the acetaldimine anions, the *syn*-preference energy is found to be substantially smaller than the value of 6.2 kcal/mol determined at 4-31G.[10]



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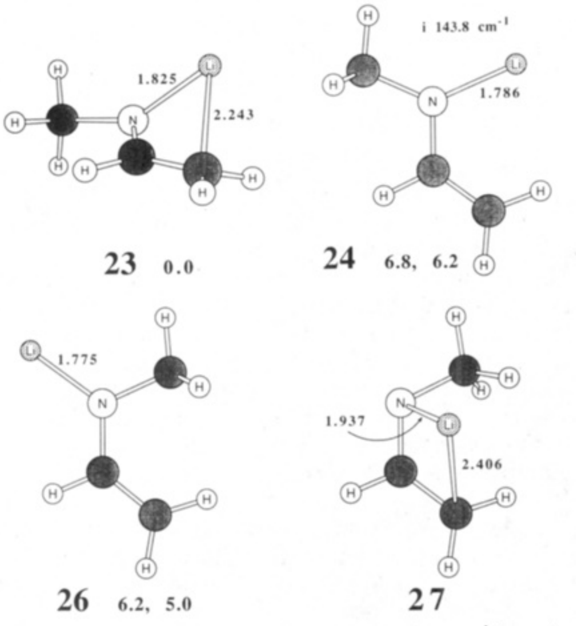
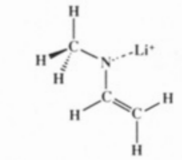


Figure 7. Structure showing how lithium coordinates the *anti*-configured *N*-methylacetaldimine in an η^3 fashion in the most stable lithium ion pair of N-methylacetaldimine, **23**. The structure of the transition state for racemization of the chiral π-complex **23** involves single N_σ coordination, **24**. Lithium coordination of the N_σ lone pair results in the most stable *syn*-configured ion pair of *N*-methylacetaldimine, **26**. Energies are given with respect to the most stable ion pair of the *N*-methylacetaldimine, **23**. There exists a local minimum for a π-coordinated lithium ion pair of the *syn*-configured *N*-methylacetaldimine, **27**.

The structure of the transition state for *syn*/*anti* isomerization of *N*-methylacetaldimine anion is shown in Figure 6. The exchange of the N hydrogen by the electron-donating methyl group increases the activation barrier to isomerization as expected (ΔE_A = 2.1 (*syn*) and 1.0 kcal/mol) but the effect is small. The energies required for the processes **19** to **20** and **20** to **19** are 21.2 and 17.4 kcal/mol, respectively, at the highest level.

Effects on Structures, *syn* Preference Energies, and the *syn*/*anti* Isomerization of the Ion Pairs. As with the lithium ion pair of the unsubstituted acetaldimine, an η^3 face-coordinated and *anti*-configured structure, **23**, has been found as the global minimum on the potential energy surface of lithium *N*-methylacetaldimine and its structure is shown in Figure 7. The LiN contacts are identical in **9** and **23**. The LiC contact and the CN bond are shortened in **23** compared to those in **9** by 0.040 Å and 0.014 Å, respectively. The pyramidalization of the CH_2 group is stronger in **23** than in **9** (dihedral angles H–C(H$_2$)–C(N)–H(CH$_2$) are 139.5° in **23** and 161.4° in **9**). Presumably, the electron-donating capability of the methyl group increases the carbanionic character of the CH_2 carbon and reduces the internal charge transfer from the CH_2 group to N.

The barrier to racemization of the enantiomeric structures **23** via the C_s-symmetric η^1-N_σ-coordinated transition-state structure **24** (Figure 7) is 6.2 kcal/mol at the highest level, 2.0 kcal/mol higher than for the racemization of the unsubstituted acetaldimine. Note that the in-plane methyl H and Li are cis with respect to the NC bond in **24**, whereas the in-plane methyl H and the N_σ lone pair are staggered in the *anti* anion. Optimization of a C_s-symmetric structure in which the in-plane methyl H and Li are trans with respect to the NC bond results in the



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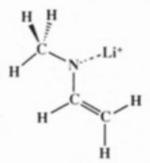

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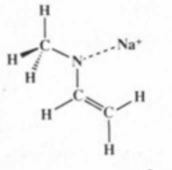
structure **25**, a second-order saddle point (i170.3 and i91.6 cm^{-1}) which is 0.9 kcal/mol higher in energy than the transition-state structure **24** (i143.8 cm^{-1}).

Li coordinates only to N in the most stable lithium ion pair of the *syn*-configured *N*-methylacetaldimine C_s-**26** (Figure 7). The relative energy of the isomeric lithium ion pairs is practically unaffected by the methyl substituent. At the highest level the *anti*-configured ion pair **23** is more stable than the *syn* isomer by 5.0 kcal/mol. The corresponding value for the lithium ion pair of the unsubstituted acetaldimine is 5.3 kcal/mol.

In contrast to the lithium ion pair of acetaldimine, there exists a local minimum for a π-coordinated ion pair formed by the *syn*-configured *N*-methylacetaldimine: The π-complex **27** (Figure 7) is 5.2 kcal/mol higher in energy than **26**.

The structure of the transition state **28** (i200.7 cm^{-1}) for *syn/anti* isomerization of the lithium ion pair of *N*-methylacetaldimine (Figure 8) is quite similar to the respective structure **16** of the unsubstituted imine. Both structures are characterized by comparatively long CN and short CC bonds of the azaallylic skeleton (Table VII). The activation energies required for the processes **26** via **28** to **23** and **23** via **28** to **26** are 10.5 and 16.9 kcal/mol, respectively, at the highest level. The corresponding values for the processes involving the isolated anions are 17.4 and 21.2 kcal/mol. The lithium cation stabilizes the vinylamide-type transition state substantially (vide infra) and the barriers to isomerization are greatly reduced under ion-pair conditions.

Comparison of the π-coordinated lithium ion pairs of the *anti*-configured acetaldimine and its *N*-methyl derivative shows that the electron-donating capability of the methyl group apparently increases the carbanionic character of the CH_2 carbon and reduces internal charge transfer from the CH_2 group to N. The same trend is found for the Na derivatives. The η^1-N_σ-coordinated structure **17** is the minimum for the sodium ion pair of the *anti*-configured acetaldimine. However, the larger carbanionic character of the CH_2 carbon in the *anti*-configured *N*-methylacetaldimine anion suffices to favor a nonplanar structure, **29** (Figure 9), to become the minimum in the substituted case. The magnitude of the interaction between sodium and the CH_2 carbon remains small, however, and **29** does not correspond to a "stable" structure. The barrier to racemization for the enantiomers **29** via the C_s-symmetric transition-state structure **30** is only 2.5 kcal/mol at the highest level. The structure **30** (i126.4 cm^{-1}) and the second-order saddle-point structure **31** relate to each other in the same way as the Li derivatives **24** and **25**. The orientation of the methyl group has practically no effect on the energy; **24** and **25** differ by no more than 0.1 kcal/mol at the highest level. The sodium ion pair of the *anti*-configured *N*-methylacetaldimine is thus best considered as an η^1-N_σ-coordinated ion pair in which the position of Na oscillates very readily.



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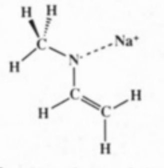

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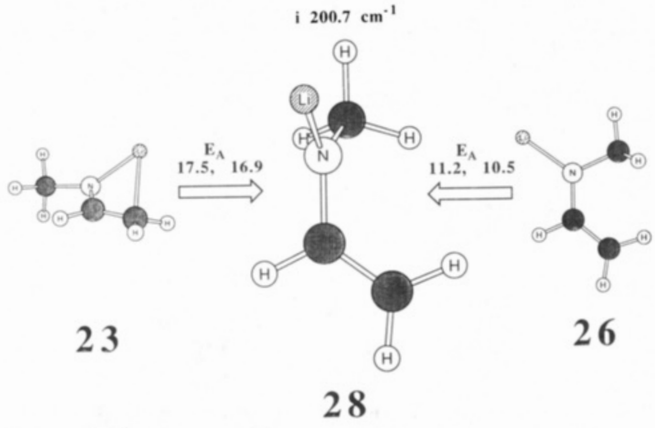

Figure 8. Structure of the transition state for *syn/anti* isomerization of the lithium ion pairs of *N*-methylacetaldimine, **28**. $E_A(syn)$ and $E_A(anti)$ are the relative energies with respect to the *syn*- and *anti*-configured lithium ion pairs **26** and **23**, respectively.

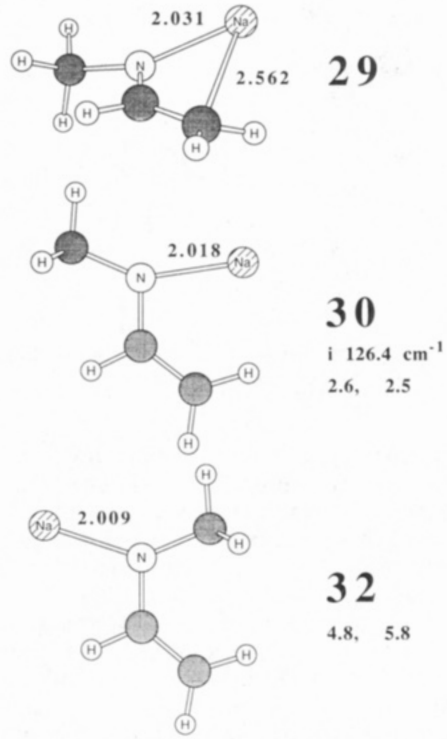

Figure 9. Global minimum for the sodium ion pair of *N*-methylacetaldimine **29** (C_1). The structure of the transition state for racemization of C_1-**29** involves single N_σ coordination, **30**. The cation engages in η^1 N_σ coordination in the only minimum found for the sodium ion pair formed with the *syn*-configured *N*-methylacetaldimine, **32**.

The only minimum for a sodium ion pair formed with the *syn*-configured *N*-methylacetaldimine anion is C_s-**32** (Figure 9). The thermodynamic preference for the *anti*-configured sodium ion pair is 5.8 kcal/mol at the highest level. Replacement of Li by Na increases the relative energy between the isomeric ion pairs by 0.8 kcal/mol in the case of *N*-methylacetaldimine, whereas a decrease of 1.9 kcal/mol has been obtained for the unsubstituted acetaldimines.

Solvation Effects on the Isomer Preference of Lithioacetaldimine. The disolvated and the trisolvated isomeric lithioacetaldimines were studied to examine the effects of primary solvation on ion-pair structure and isomer preference energies. All of these solvated ion pairs were optimized in overall C_s symmetry with N_σ η^1 coordination of the metal. While the *syn*-configured unsolvated ion pair **14** involves such N_σ η^1 coordination, the most

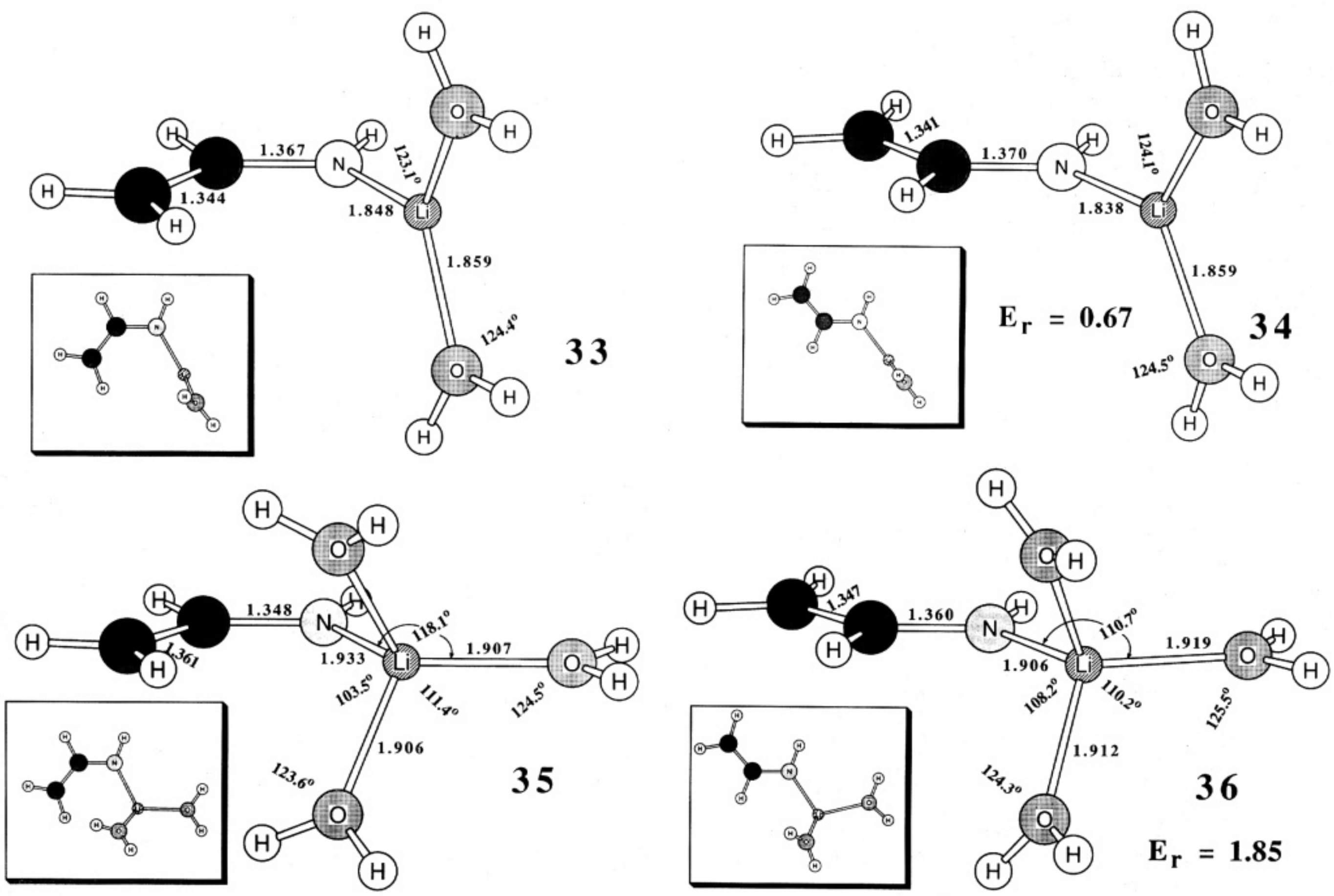

Figure 10. Optimized structures of disolvated and trisolvated isomeric lithioacetaldimines as determined as the RHF/3-21G level. Relative energies given are those determined at RHF/6-31+G*//RHF/3-21G in kcal/mol.

stable *anti*-configured ion pair **9** prefers an η^3 face coordination. However, in the solvated system—and in the trisolvated system in particular—it is more likely that an $N_\sigma\ \eta^1$ lithium coordination will be realized as such a mode of coordination allows for a better coordination of lithium by the solvent molecules that should easily compensate for the structural change from a type **9** ion pair to the type **10**. Additionally, the $LiOH_2$ fragments all were kept in local C_{2v} symmetry. The advantage of this constraint is that unwanted H-bonds are prohibited. The optimized structures thus obtained at the RHF/3-21G level are shown in Figure 10 and they should be good models for ether solvation. Energies were also calculated at the RHF/6-31+G*//RHF/3-21G level and the relative energies determined at this level are given in Figure 10.

In both of the disolvated systems *anti*-**33** and *syn*-**34**, the lithium is coordinated in a trigonal planar fashion and, in the trisolvated systems *anti*-**35** and *syn*-**36**, the lithium is coordinated in a only slightly distorted tetrahedral fashion. In all of these complexes, replacement of the water molecules by ether molecules is not expected to cause large steric effects, that is, these models appear suitable to model ether solvation. Lithium solvation elongates the Li–N bond lengths in all cases but has comparatively little effects on the structures of the lithioacetaldimines (Table VI and VIII).

As with the unsolvated lithioacetaldimines, we find an *anti* preference for the di- and for the trisolvated monomers. Note that the constraint to overall C_s symmetry would reduce the *anti*-preference energy. At the RHF/6-31+G*//RHF/3-21G level *anti* preference energies of 0.67 (disolvation) and 1.85 (trisolvation) kcal/mol are found.

Table VIII. Metal Affinities

molecule			3-21PG		6-31+G*	
A	B	M	SCF	SCF+ZPC	SCF	SCF+ZPC
9	**2**	Li	172.5	169.8	164.8	162.1
14	**1**	Li	168.2	165.6	161.2	158.6
17	**2**	Na	155.3	153.1	138.4	136.2
18	**1**	Na	149.1	147.1	132.1	130.1
23	**20**	Li	174.7	171.9	168.8	165.9
27	**19**	Li	154.7	152.7	152.4	150.3
29	**20**	Na	158.2	155.8	137.5	135.1
32	**19**	Na	150.4	147.7	128.0	125.3

[a] The metal affinity of ion pair A is given with respect to the anion B and the cation M in kcal/mol.

Mechanistic Consequences. Free Ions versus Ion Pairs. In solvents with high dielectric constants the metalated enolate derivative is completely dissociated into free ions and the relative stability of the isomeric imine carbanions is expected to determine the regiochemistry of their reactions with electrophiles. Our theoretical results show preferences for the *syn*-configured isolated carbanions of acetaldimines in agreement with the experimentally observed regiochemistry of imine carbanions in solvents such as DMSO.[8] Metalated imines occur predominantly as ion pairs and aggregates in solvents of low polarity such as THF and the consideration of such ion pairs is clearly indicated in discussions of reaction mechanisms. The Li and Na affinities of the imine carbanions are summarized in Table VIII.

Ion-Pair Topologies. The most stable unsolvated and monomeric ion pair formed between Li or Na and a substituted or unsubstituted *syn*-configured acetaldimine anion has C_s symmetry and the metal cation coordinates solely to the N_σ lone pair. Ion-pair structures in which the cation engages in a π-coordination of the *syn* anion are either higher in energy or do not correspond to local minima on the potential energy surface. Two different modes of coordination have been found for the equilibrium structures of the ion pairs formed with the *anti* anions: the metal cation either coordinates to the azaallylic system in a π-fashion or it coordinates solely to N. The activation barriers to racemization are small for all of the π-coordinated ion pairs formed with the *anti*-configured acetaldimines and these intermediates are therefore best considered as η^1-N_σ-coordinated ion pairs in which the metal oscillates readily between enantiomeric positions. The magnitude of the activation barrier depends on the substituent on N and on the nature of the gegenion: The activation barrier is smaller for the unsubstituted acetaldimine derivatives than for the *N*-methylacetaldimine derivatives (e.g. ΔE_A(**23**–**9**) = 2.0 kcal/mol) and it is smaller for the Na ion pairs than for the Li ion pairs (e.g. ΔE_A(**23**–**29**) = 3.7 kcal/mol). For the sodium ion pair of the unsubstituted acetaldimine the activation barrier vanishes and one symmetric equilibrium structure (**17**) results instead of a pair of enantiomers (e.g. **9**, **23**, and **29**). The low values of the activation barriers to racemization of the chiral ion-pair structures makes it questionable whether these π-coordinated structures would survive if solvent molecules were included in the calculation. The solvation enthalpy is expected to be higher for those ion pairs in which the metal is coordinated the least and solvation is therefore expected to favor ion pairs with η^1 N_σ coordination. Ion-pair formation reverses the relative stabilities of the *syn*/*anti* isomers compared to the imine carbanions; the calculations show a thermodynamic preference for the *anti*-configured unsolvated and monomeric metalated derivatives of acetaldimine and this thermodynamic *anti* preference persists in the di- and trisolvated systems.

Aggregation. Spectroscopic evidence indicates that the dominant species in solution have the *syn* configuration.[9] This experimental finding and the computed isomer stabilities of the monomeric ion pairs suggest that metalated imines are aggregated in solution (and that aggregates formed by the *syn*-configured ion pairs must be more stable than aggregates that contain *anti*-configured monomeric units). This theoretical result also agrees with recent experimental aggregation studies of lithiated cyclohexanone phenylimine by Collum et al.[40] NMR spectroscopy shows that these lithioimines form dimers in solution. Similar aggregation behavior had earlier been reported for lithioamides by the same group.[41,42] Considering that the anions formed from imines are more like amide anions than carbanions (vide supra), this similarity between the lithioimines and the lithioamides is, in fact, not surprising. The activation barriers for *syn*/*anti* isomerization of the monomeric lithium ion pairs of acetaldimine carbanions have been shown to be lower than 17 kcal/mol and either of the monomeric *syn*- or *anti*-configured ion pairs is thus readily available as a monomeric unit for the formation of aggregated species. The difference between the measured and the calculated barriers to rotation around the CC bond provides further evidence for the importance of ion-pair aggregation in solution. For lithioaldimines, barriers of 17–23 kcal/mol have been measured[18] while our work shows that the activation barrier for CC rotation in the lithium ion pair of acetaldimine is only about 10 kcal/mol. Semiempirical calculations of dimeric aggregates show a C_{2h}-symmetric dimer with coplanar anions and with the out-of-plane cations bridging between the N atoms as the most stable structure for dimeric aggregates formed by two *syn*-configured ion pairs.[43,44] In such aggregates the cations are less available for stabilization of the charge in the carbanionic transition-state structures for rotation of the CH_2 group (vide supra). Aggregation should therefore result in increased barriers to rotation around the CC bond compared to monomeric ion pairs. The catalytic effect of hexamethylphosphoramide (HMPA) on the equilibration of CC isomers of metalated propanaldimine[20] could also be caused by ion-pair aggregates. The strongly chelating HMPA may promote the interconversion of different aggregates and the rate for CC isomerization may be faster in small aggregates or monomeric ion pairs than in larger aggregates.

Nature of the Reactive Species. Monomeric ion pairs have in general been considered in those discussions of reactive mechanisms that account for the importance of metal chelation in the intermediate. Monomeric ion pairs could still be the *reactive species* although the present study suggests that metalated imines are aggregated under typical reaction conditions. However, the *structures* presented provide strong evidence that the *monomeric* ion pairs cannot account for the experimentally observed stereochemistry of the reaction products and therefore *monomeric ion pairs are probably not the reactive species* in reactions with electrophiles.

The regiospecific addition of an electrophile to a *monomeric* ion pair leading to the *syn*-configured product would only be possible if the reaction were kinetically controlled. However, the calculated structures of the monomeric ion pairs show no advantage for the reaction of the *syn*-configured ion pair compared to the *anti*-configured isomer. In contrast, the addition of an electrophile to the *anti*-configured ion pair should be kinetically and thermodynamically favored because the gegenion could maintain its coordination to nitrogen and additionally coordinate to the nucleophile of the electrophilic reagent and thus stabilize the product and the transition state. In the *syn*-configured ion pair the cation is far away from the reactive center and stabilizing proximity effects[45] between the cation and the electrophile are certainly less important. Ab initio calculations of the products of reactions of isomeric lithioacetaldimines with formaldehyde[46] show the *anti* product to be more stable than the *syn* product. In the *anti* product the cation takes part in a relatively unstrained six-membered ring and coordinates to the N_σ lone pair and to the alkoxy oxygen. In the *syn* product the cation no longer resides at the N_σ lone pair but coordinates to the CN bond in a π-fashion. The orientation of the alkoxy O toward the cation leads to a strained ring in the

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(40) Gilchrist, J. H.; Harrison, A. T.; Fuller, D. J.; Collum, D. B. *J. Am. Chem. Soc.* **1990**, *112*, 4069.

(41) (a) Galiano-Roth, A. S.; Collum, D. B. *J. Am. Chem. Soc.* **1989**, *111*, 6772. (b) Galiano-Roth, A. S.; Michaelides, E. M.; Collum, D. B. *J. Am. Chem. Soc.* **1988**, *110*, 2658.

(42) DePue, J. S.; Collum, D. B. *J. Am. Chem. Soc.* **1988**, *110*, 5518, 5524.

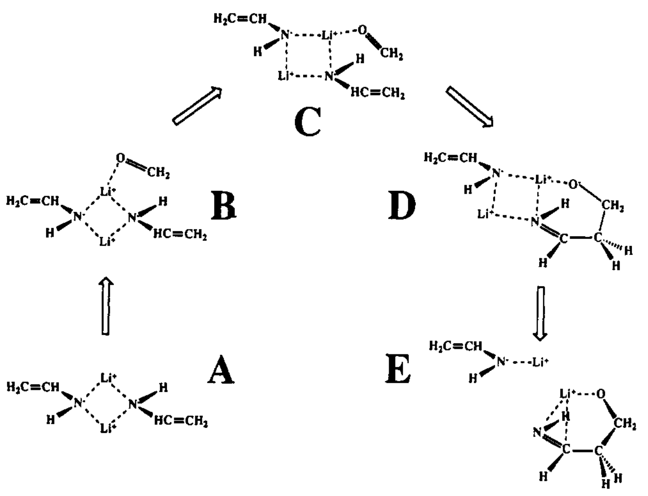
(43) MNDO calculations of solvated and unsolvated aggregates of lithioacetaldimine: Lee, K. H.; Streitwieser, A., Jr., unpublished results.

(44) In the most stable dimer formed by two *anti*-configured ion pairs each of the cations coordinates to one of the anions in a π-fashion and additionally to the CH_2 carbon of the other anion. The *anti* dimer is favored over the *syn* dimer at the MNDO level (ref 43) but the *anti*-preference energy is reduced. However, the relative stabilities of the *syn* and *anti* dimers may be in error due to the severe overestimiation of the strength of the LiC contacts in the *anti* dimer. For a discussion of methodological deficiencies associated with MNDO calculations of lithium ion pairs of acetaldoxime carbanions, see ref. 27.

(45) Beak, P.; Meyers, A. *Acc. Chem. Res.* **1986**, *19*, 356 and references therein.

(46) Krom, J.; Streitwieser, A., Jr., unpublished results.

Scheme III



syn product. *The assumption of monomeric ion pairs as the reactive species is thus inconsistent with the regioselectivity of the reaction of electrophiles with metalated imines.*

The theoretical results suggest that reaction leading to the *syn* product is possible only if ion-pair aggregates exist in solution and also are the *reactive* species. A possible reaction mechanism for the reaction of the smallest aggregate,[43] the dimer (vide supra), of the *syn*-configured lithioacetaldimines with formaldehyde is shown in Scheme III. In the dimer (A) the cation is out of the plane of the anions and in a significantly better position for stabilizing interactions with the approaching electrophile (B) compared to the monomers. A deformation of the dimer formed between the cations and the nitrogen atoms of the two anions in the dimer could allow one of the cations to stabilize the developing charge of the nucleophile X^- along the reaction pathway (C) and in the product (D). The deformation of the dimer would place each of the cations along the directional axis of the N lone pair of one of the imine anions[47] and is therefore expected to cause but little destabilization of the dimer. Fragmentation of the aggregate (E) after the formation of the new bond to the α-carbon results in the *syn*-configured product and an unreacted ion pair. The key feature of this mechanism consists in the *catalysis of the reaction of one monomeric ion pair by another ion pair.* Hence, the formation of the *syn*-configured product under kinetic control relies on the presence of *some* ion pair that is capable of such "ion-pair catalysis".[48] The case for which the dimeric aggregates are the reactive species is therefore the special case for which the necessary ion pair catalyst happens to be identical with the reactant, that is, the reaction is autocatalytic.[49]

Alkyl- versus Hetero-Substituted Imine Derivatives. The results of this study allow an analysis of the structural and mechanistic consequences of the second heteroatom in *hetero*substituted imine derivatives, such as oxyimines and hydrazones. Our ab initio studies of metalated oxime carbanions showed that all equilibrium structures are chiral and that the cation is always in a bridging position. All stationary structures in which the metal coordinates in an η^1 N_σ fashion have been shown to be saddle points.[29] For the lithium ion pair of the *anti*-configured acetaldoxime carbanion two almost isoenergetic minima have been found.[28] In one of these structures Li bridges the NO bond and there is, of course, no analogue to this structure in the case of the imine derivative. However, the topology of the other ion pair of the *anti*-acetaldoxime carbanion and of the *anti*-configured lithioacetaldimine are analogous; Li bridges between N and the CH_2 carbon in a π-fashion. An important difference between the bonding situation in the two cases is revealed by the activation barriers to racemization. This barrier is significantly larger in the case of the oxime derivative (12.3 kcal/mol) compared to the metalated imine (4.2 kcal/mol). The increased barrier to racemization for the oxime ion pair can be attributed to two effects. Electron-electron repulsion between the O lone pairs and the electron density at the oxime N counteracts charge accumulation at the oxime N by internal charge transfer from the CH_2 carbon. The LiN distance is longer and the LiC contact is shorter in the oxime derivative compared to the metalated imine. The somewhat stronger LiC contact in the oxime is thus one of the factors that contributes to the larger activation barrier to racemization. More importantly, additional stabilization of the oxime ion pair by polarization of O lone pair electron density toward the gegenion is only possible if the cation is in a π-coordinating position. The loss of this electrostatic stabilization along the racemization pathway increases the activation barrier. The effect of the oxime O on the structures of the ion pairs of the *syn*-configured oxime carbanion as compared to the *syn*-configured metal derivatives of the imines is more direct; the availability of the oxime O for chelation changes the topology of the metal coordination. The η^2 NO bond coordination is so strong in the oxime derivatives that structures with single N_σ coordination, minima in the case of the imine derivatives, can no longer compete and they are in fact saddle points.[29] The *syn*-preference energy is 3.0 kcal/mol for the Li derivatives of acetaldoxime carbanions[29] and the *anti*-preference energy is 5.3 kcal/mol for the lithioacetaldimine at the same level. The presence of the oxime O thus stabilizes the *syn*-configured isomer 8.3 kcal/mol *more* than the *anti* isomer. The additional stabilization of the *syn*-configured ion pair by the oxime O is larger for Na since the *syn*-preference energy of metalated oximes increases with the size of the cation while the *anti* preference of the imine ion pairs stays about the same or decreases slightly upon replacement of Li by Na.

Conclusion

The π-conjugated *syn*- and *anti*-configured azaallyl anions of the acetaldimines are minima. The *syn* anions are thermodynamically favored compared to the *anti* isomers and the *syn* preference energies account for the regiochemistry of electrophile additions under chemical conditions that favor free ions.

Typical conditions for the generation and reaction of metalated imines favor ion association. The structures of the Li and Na ion pairs of the *syn*-configured acetaldimines all involve single N_σ coordination and in the corresponding *anti* isomers the gegenion coordinates to the azaallylic

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(47) A similar arrangement has been found in the solid state, see ref 25.

(48) For an example of a "mixed" dimer, see ref 42.

(49) The proposed mechanism allows for a prediction concerning possible manipulations of the regiochemistry of electrophilic additions to metalated imines under conditions that result in monomeric ion pairs as the predominant species in solution. The theoretical results suggest that the predominating percentage of the ion pairs would be *anti*-configured in this case. Ion-pair catalysis of the small amount of the *syn*-configured ion pairs present (An *anti*-configured ion pair would be perfectly suitable as the assisting ion pair in the reaction leading to the *syn* product.) and direct reaction of the *anti*-configured ion pair would result in a mixture of *syn* and *anti* products in a certain ratio. In all of those cases where the *anti* products were formed in significant amounts, it should be possible to reduce the amount of the *anti* product by addition of a metal salt suitable for enhancing the formation of the *syn* product by ion-pair catalysis.

system either in a π-fashion or exclusively to nitrogen. The racemizations of enantiomeric π-complexes of the *anti* anions are fast processes even at low temperatures. The activation barrier is smaller for the unsubstituted acetaldimine derivatives than for the *N*-methylacetaldimine derivatives and it is smaller for ion pairs formed with Na than with Li. For the sodium ion pair of the unsubstituted acetaldimine, the activation barrier vanishes and one symmetric equilibrium structure results. *Ion-pair formation reverses the relative isomer stabilities*; in all cases a preference for the *anti*-configured monomeric ion pairs has been found. Our studies of the solvated lithioacetaldimines show that the *anti* preference persists if primary solvation is accounted for. The *anti*-preference energies found for the ion pairs and the experimentally determined configuration of the metalated intermediate show that metalated imines are aggregated under typical reaction conditions and that aggregation favors the *syn* configuration of the monomeric units. The activation barriers for *syn*/*anti* isomerization of the ion pairs are small and each of the isomeric ion pairs is thus readily available for the formation of aggregated species.

The relative stabilities and the structures of the *monomeric* ion pairs lead to the inescapable conclusion that metalated imines are aggregated in ether solutions and, moreover, that the *monomeric ion pairs cannot be the reactive species* in reactions with electrophiles. The kinetically controlled regioselective formation of the *syn*-configured product cannot be accounted for by the structures of the *syn*-configured ion pairs. Ion-pair catalysis of the reaction of the *syn*-configured ion pair has been proposed as the mechanism responsible for the preferential formation of the *syn* product. In the absence of other metal salts, a second ion pair of the metalated imine is required as ion pair catalyst, that is, the reaction is autocatalytic and the dimeric ion-pair aggregate becomes the smallest conceivable reactive species. We have tested this postulated mechanism of the dimer reaction at the ab initio level and found that this mechanism indeed provides a consistent explanation for the experimentally observed reaction stereochemistry.[50]

The mechanism responsible for the regioselective formation of a new bond to the α-carbon in the *syn* position of a metalated imine thus appears to be entirely different from the mechanisms thought to be operative in similar reactions of other metalated N derivatives of carbonyl compounds. Metalated hydrazones,[51] metalated oxime ethers,[27-29] and dimetalated oximes[52] all show a thermodynamic preference for the formation of the *syn*-configured ion pair. The presence of another heteroatom adjacent to the nitrogen of the azaallylic skeletons results in structures in which (one of) the gegenion(s) π-coordinates the face of the (di)anion and the cation is thus readily available for stabilization of the reaction transition state and the product. In these cases the preferential formations of the *syn*-configured reaction products can readily be understood on the basis of the properties of the *monomeric* ion pairs and these ion pairs are likely to be the reactive species even if aggregation is important.[26,27] In contrast, in the case of the metalated imines cooperative effects are necessary to allow for the regioselectivity of the electrophile addition. Ab initio studies of the dimeric aggregates of the isomeric lithium ion pairs and of their reactions with electrophiles are currently in progress to further explore the reaction mechanism. Preliminary results of these studies fully support the ideas presented here.

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Registry No. 1, 78507-80-9; 9, 136476-97-6; 17, 136476-98-7; 19, 136476-94-3; 23, 78357-14-9; 29, 136476-99-8; 33, 136476-95-4; 35, 136476-96-5.

Supplementary Material Available: Optimized structures, energies, and vibrational frequencies (and transition vectors) of stationary points of (solvated) isomeric anions of acetaldimine and *N*-methylacetaldimine and their ion pairs with lithium and sodium (16 pages). Ordering information is given on any current masthead page.

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(50) Glaser, R.; Hadad, C.; Wiberg, K.; Streitwieser, A. *J. Org. Chem.*, following paper in this issue.

(51) Studies of the lithium ion pairs of isomeric carbanions of acetaldehyde hydrazone: Glaser, R.; Streitwieser, A., unpublished results.

(52) Glaser, R.; Streitwieser, A. Jr. *J. Org. Chem.* 1989, *54*, 5491.