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The Interplay of Thio(seleno)amide/Vinylogous Thio(seleno)amide "Resonance" and the Anisotropic Effect of Thiocarbonyl and Selenocarbonyl Functional Groups

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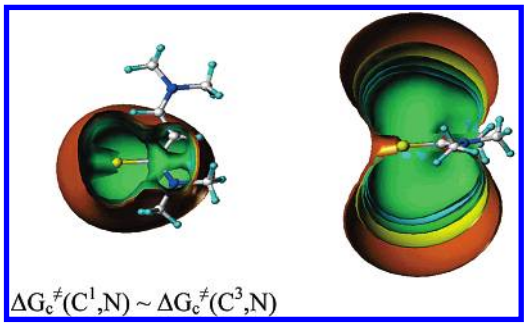
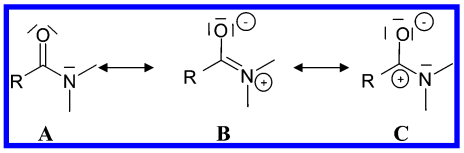


Amino-substituted thio(seleno)acrylamides **1**−**4** were synthesized and their ^{1}H and ^{13}C NMR spectra assigned. Both the NMR data and the results of theoretical calculations at the ab initio level of theory were employed to elucidate the adopted structures of the compounds in terms of *E*/*Z* isomerism and *s-cis*/*s-trans* configuration. In the case of the asymmetrically N(Me)Ph-substituted compounds, ab initio GIAO-calculated ring current effects of the *N*-phenyl group were applied to successfully determine the preferred conformer bias. The restricted rotations about the two C−N partial double bonds were studied by DNMR and the barriers to rotation ($\Delta G_c^{\ddagger}$) determined at the coalescence temperatures, and these were discussed with respect to the structural differences between the compounds. The barriers to rotation were also calculated at the ab initio level of theory where the best results ($R^2 = 0.8746$) were obtained only with inclusion of the solvent at the SCIPCM-HF/6-31G* level of theory. The calculations also provided means of assessing structural influences which were not available due to inaccessible rotation barriers. By means of natural bond orbital (NBO) analysis of **1**−**4**, the occupation numbers of nitrogen lone pairs and bonding/antibonding π/π^* orbitals were shown to quantitatively describe thio(seleno)amide/vinylogous thio(seleno)amide "resonance". Finally, the thio(seleno)carbonyl anisotropic effect was quantitatively calculated by the GIAO method and visualized by isochemical shielding surfaces (ICSS). Only marginal differences between the two anisotropic effects were calculated and are therefore of questionable utility for previous and future applications with respect to stereochemical assignments.

Introduction

The restricted rotation about the partial C−N double bond in amides, as simple models for the peptide bond in proteins, has been extensively studied.[1] The traditional notion of "amide resonance" **A** ↔ **B** (see Scheme 1) as

SCHEME 1



the cause of the barrier to rotation about this bond has been questioned[2] by Wiberg et al., who determined by theoretical ab initio studies that the major contributor to the barrier arises not from charge transfer to the oxygen, but rather by charge transfer between nitrogen

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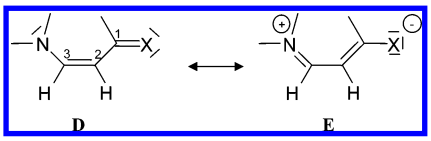
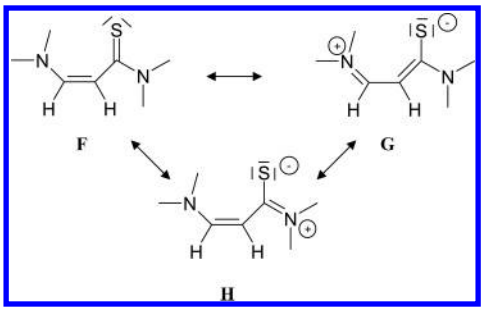
and carbon (see also resonance structure **C** in Scheme 1). The barrier to rotation in the corresponding thioamides, however, is larger, and thus, the traditional concept of charge transfer to the oxygen is more appropriate,[3,4] though the situation is more consistent with the view that thioamides behave as thioformylamines.[5] Based on X-ray analyses and more sophisticated ab initio calculations, however, the resonance model is indeed quite adequate to explain the properties of amides,[6,7] thioamides,[8,9] and also selenoamides.[10] When studied under similar conditions, the larger rotation barriers of thioamides[11,12] when compared with those of the corresponding amides were shown to be linearly dependent,[13] thus implying that the same mechanism and electronic source is the underlying cause for the dynamic process in both cases. The charge-transfer $n_N \rightarrow \pi^*_{C=X}$ (X = O, S, Se) has been identified as the main component responsible for the height of the barrier which linearly increases (O < S < Se) with participation of resonance structure **B**.[14,15] This is also accompanied by opposing migration of σ charge density, thus rendering the integrated atomic charges smaller than expected from pure π delocalization.[16]

Similarly, the corresponding barrier to rotation in vinylogous amides[17−19] and thioamides[20−24] (see Scheme 2) has been discussed in terms of the resonance structure **E** participating in the ground state to a large degree with respect to the restricted rotations about the C_1-C_2, C_2-C_3, and C_3-N partial double bonds. Again, the rotation barrier was shown to be higher in the vinylogous thioamides than in the corresponding amides.[20,24] When both thioamide and vinylogous thioamide moieties are in the same structure, the two rotation barriers were shown to be of approximately equal size (**G** and **H** in Scheme 3).[25] Recently, however, this vinylogous amide resonance was questioned when *N*,*N*-dimethylaminoacrylnitrile was better regarded as a vinylamine substituted with electron-withdrawing substituents,[26] even if the rotation barrier about the C_2-C_3 bond could not be measured (only two substituents on the C=C double bond are insufficient to reduce the barrier enough for experimental measurement).[27] Addition of another cyano group, $(NC)_2C=C(Ph)NMe_2$, further increases the barrier to rotation about the C−N bond and corroborates the participation of a resonance structure similar to **G** (cf. Scheme 3).[28]

SCHEME 2



SCHEME 3



Because of the equivocal ties mentioned, a larger variety of amino-substituted thioacrylamides **1**, selenoacrylamides **2,** and their azaanalogues **3** and **4** (cf. Scheme 4; it should be mentioned that **1**−**4** could be also classified as vinylogous urea and azavinylogous urea derivatives, respectively) were synthesized, and their dynamic behavior was studied experimentally by dynamic NMR spectroscopy and theoretically by ab initio MO calculations at various levels of theory. To investigate the electronic interactions between the various molecular orbitals in the compounds studied, natural bond orbital (NBO) analysis[29] was performed. The investigation of **1**−**4** provides a quantitative understanding of the substituent effects on the rotational barriers as well as the rotating vinylogous thio- and selenoamide systems themselves by providing valuable information on bond energies, electron occupancies, and bond/antibond interactions.

Results and Discussion

^{1}H and ^{13}C NMR Spectra. The signals in the ^{1}H NMR spectra of **1**−**4** were generally well dispersed, and con-

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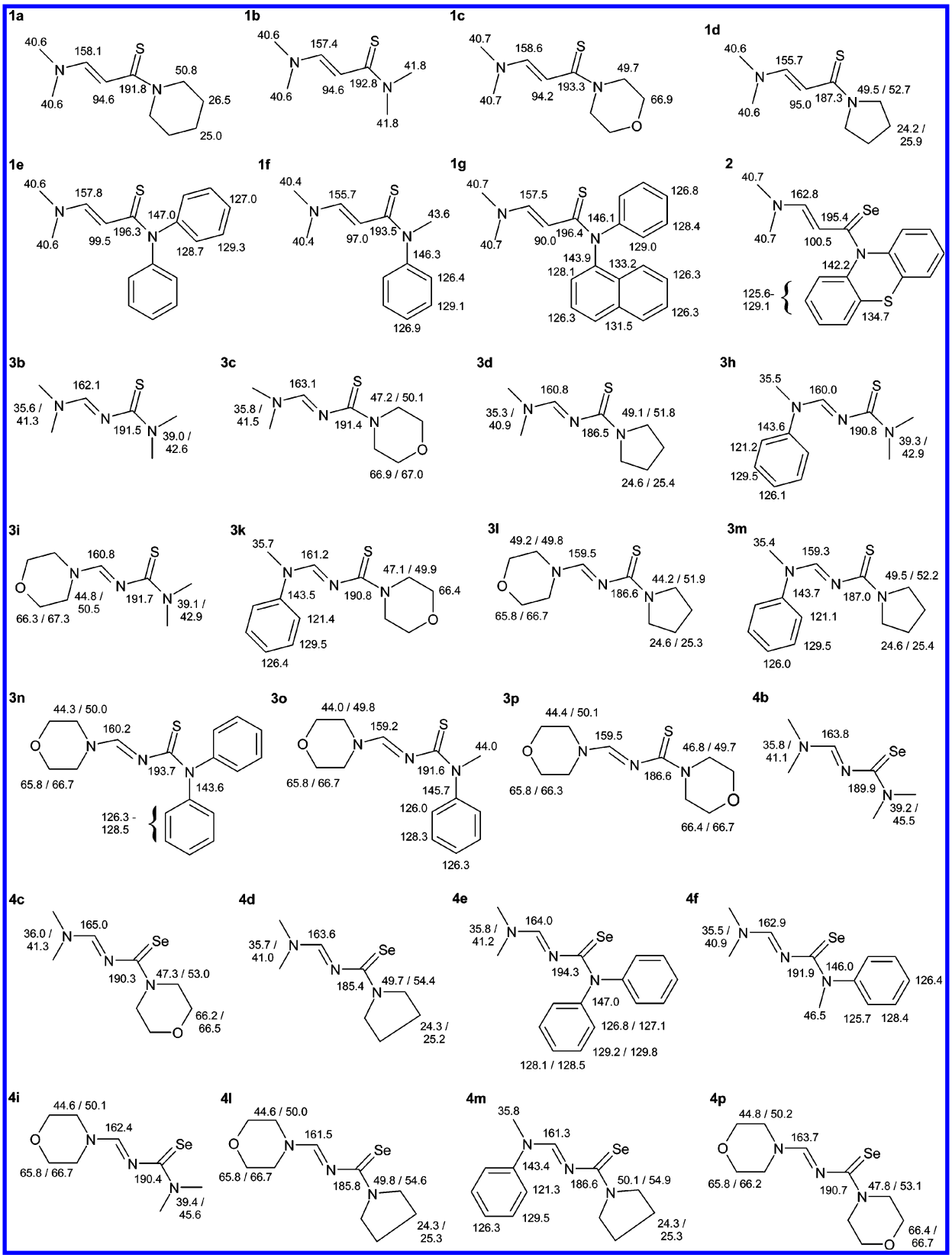
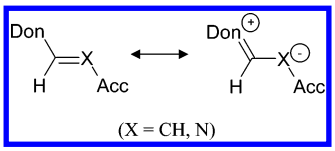
SCHEME 4

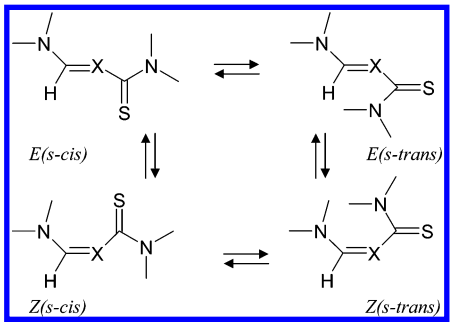


sequently, in such cases they were easily assigned (Table S1 in the Supporting Information). Due to the push−pull effect,[27] the chemical shifts of H-1 and H-2 in **1** and **2** are extremely deshielded (δ_{H-1} = 8.01−8.43 ppm) and shielded (δ_{H-2} = 4.88−5.55 ppm), respectively. The vicinal coupling constant between these two protons lies in the range of 11.5−11.9 Hz; hence, an *E* configuration for **1** and **2** can be assigned[25] since in the corresponding *Z* configuration this coupling constant has been shown to be less than 9 Hz.[25] In the case of the imino-substituted

SCHEME 5



SCHEME 6



analogues **3** and **4**, H-1 (δ_{H-1} = 8.70−9.14 ppm) is deshielded even more due to additional substituent effects. Also readily assignable were the proton signals of the *N*-alkyl substituents. Coupling information was corroborated by COSY spectra and spatial information facilitated by NOESY spectra.[30] The aromatic protons in the $N(Ph)_2$-substituted thio(seleno)acrylamides **1e** and **3n** resonate in a very narrow range, and consequently, the ortho, meta, and para protons could not be discriminated. The same effect was observed for the N(Me)Ph analogue **4f**; in the case of **3h**, **3k**, **3m**, and **4m**, the meta protons could be differentiated from the multiplets of the ortho and para protons. Finally, in the case of **1f** and **3o**, all three proton types were well separated and therefore assignable.

The ^{13}C NMR spectra of **1**−**4** were assigned by the standard application of APT, HMQC and HMBC spectra (Table S2, Supporting Information).[30] The *ipso* and C=S/C=Se carbons were readily discerned as they displayed vicinal/geminal C,H connectivities to nearby protons (e.g., ortho or H-1/H-2 protons, respectively). The ^{13}C resonances for all compounds examined resonated well within the typical ranges anticipated; only C-1 and C-2, the carbons of the central C=C partial double bond in **1** and **2**, resonated at extreme positions for sp^2-hybridized carbon atoms due to the push−pull effect whereby C-1 is strongly deshielded and C-2, conversely, is strongly shielded (cf. Scheme 5).[27]

Structural Study. The scalar vicinal H,H trans coupling in **1** and **2** (vide supra) was the only structurally discriminating NMR parameter in the compounds studied. Whereas the exchange phenomena observed for the NR_2 substituents could be interpreted as a result of restricted rotation about the partial C_1−N and C_3−N double bonds (vide infra), additional information by NMR was not obtained concerning *E*/*Z* isomerism in **3** and **4**, nor regarding *s-cis*/*s-trans* isomerism in **1**-**4** (cf. Scheme 6); the corresponding equilibria are evidently too one-sided and only single anancomers are present. Previously, by a lanthanide-induced shift study,[25,31] the *E(s-cis)* configuration was identified as the preferred configuration in similar compounds. To corroborate this previous assignment[25,31] and to clarify the open structural questions, the amino-substituted thio(seleno)acrylamides **1**−**4** were also studied quantum chemically: the four isomers/rotamers (cf. Scheme 6) were calculated and examined with respect to their relative energies.

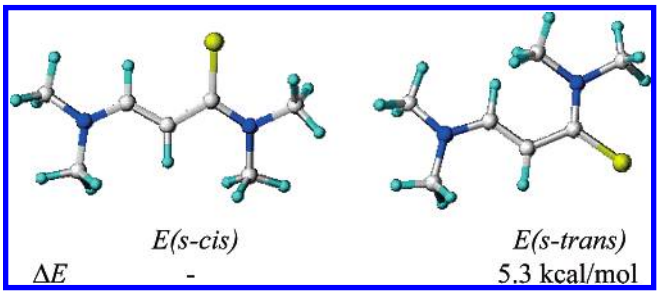


FIGURE 1. Possible isomers of the amino-substituted thioacrylamides and their relative energies.

TABLE 1. Relative Energy Differences for the Isomers of Amino-Substituted Thio(seleno)acrylamides 1−3 As Obtained by ab Initio Quantum Chemical Calculation at the HF/6-31G* Level of Theory

compd	Δ*E*(*s-cis*,*s-trans*) (kcal/mol)
1a	4.6
1b	5.3
1c	4.8
1d	8.9
1e	6.2
1f	6.9
1g	7.2
2	8.3
3b	24.6
3n	20.0

In the amino-substituted thio(seleno)acrylamides **1** and **2**, only the *E(s-cis)*/*E(s-trans)* isomers were calculated, the *Z* isomers having been unequivocally excluded on the basis of the observed value of the vicinal H,H trans coupling constants. As expected, the *E(s-cis)* isomers proved to be strongly preferred and should represent the structures as given experimentally by NMR (cf. Table 1 and Figure 1). The same result was obtained for the imino analogues **3** and **4**, but since appropriate scalar coupling was lacking, additionally the corresponding *Z(s-cis)* and *Z(s-trans)* isomers were also examined. However, local minima for both *Z(s-cis)* and *Z(s-trans)* isomers could not even be obtained due to steric reasons and again the same result (cf. Table 1) was obtained, viz. the *E(s-cis)* configuration proved to be the preferred isomer (see Figure S1, Supporting Information).

In the case of N(Me)Ph asymmetrical substitution, compounds **1f**, **3h**, **3k**, **3m**, **3o**, **4f**, and **4m** were obtained; in addition, there are another two conformers as a result of the restricted rotation about the C_1−N and C_3−N partial double bonds (see Scheme 7). On the NMR time scale within the temperature range of the present system, exchange phenomena were not observed (vide infra) and because the second C−N barrier to rotation is likely to be very similar to the rotation barriers in the other compounds studied, there was only one conclusion possible: the presence again of only one preferred conformer. The ab initio calculation of the corresponding conformers provided *N,Ph(s-trans)* conformers for compounds **3h**,

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SCHEME 7

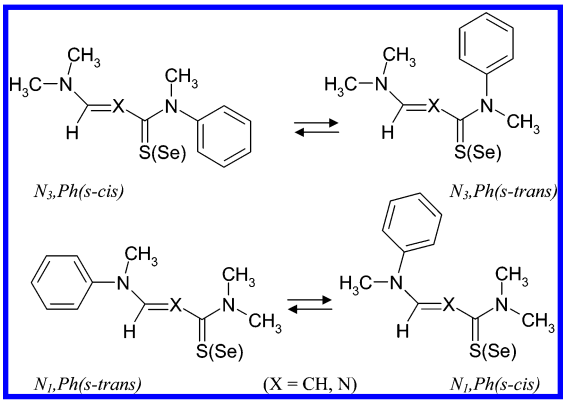

TABLE 2. Relative Energies of Conformers as a Result of Restricted Rotation about the C−N Partial Double Bonds As Obtained by ab Initio Quantum Chemical Calculations at the HF/6-31G* Level of Theory

compd	$N^{1/3}$,Ph(*s-trans*) (a.u.)	$N^{1/3}$,Ph(*s-cis*) (a.u.)	ΔE(*s-trans,s-cis*) (kcal/mol)
1f	−970.114	−970.108	4.063
3h	−986.136	−986.132	2.283
3k	−1137.898	−1137.891	4.425
3m	−1063.052	−1063.048	2.166
3o	−1137.912	−1137.909	1.739
4m	−3063.116	−3063.113	2.105
4f	−2986.199	−2986.196	1.641

3k, **3m,** and **4m** (see Figure S2, Supporting Information) and *N_3,Ph(s-trans)* conformers for compounds **1f**, **3o**, and **4f** (see Figure S3, Supporting Information). Obviously, the phenyl, due to rotation about the N−C_{ipso} bond, can elude steric hindrance better than methyl. However, except for **1f** and **3k**, the energy differences, at the ab initio level of theory (cf. Table 2), between the two conformers proved to be only a few kcal/mol, and thus a fast conformational equilibrium consisting of the two conformers could not be excluded completely. Therefore, another NMR method was employed to corroborate these conclusions.

Ab Initio MO Calculation of the Ring Current Effect of *N*-Phenyl Substituents. Recently, Klod and Kleinpeter[32] reported the ab initio MO calculations of the anisotropic effects of a number of functional groups and the ring current effect of aromatic/heteroaromatic moieties. The ring current effect of phenyl can be visualized as isochemical shielding surfaces (ICSS) and was employed to distinguish the conformers depicted in Figures S2 and S3 in the Supporting Information (e.g., in Figure 2 the orange ICSS represents shielding of −0.1 ppm at ca. 9 Å from the center of the molecule). The conformers of **1f** and **3h** are depicted in Figure 2 with various ICSS emanating from the *N*-phenyl group and their resultant effects on the protons H-1 and H-2 and of the N-1(3) methyl. The corresponding chemical shift variations due to this ring current effect were compared with the experimentally obtained chemical shift differences for the corresponding alkyl-substituted analogues (e.g., **1f** is compared with **1b**, etc.). Unequivocally, the agreement of the phenyl ring current effects in *N_1,Ph(s-trans)* and *N_3,Ph(s-trans)* and the experimental chemical shift differences of H-1 and H-2 and of the *N*-methyl protons corroborate the above assertion that these conformers are the preferred ones in the N(Me)Ph-substituted thio(seleno)acrylamides.

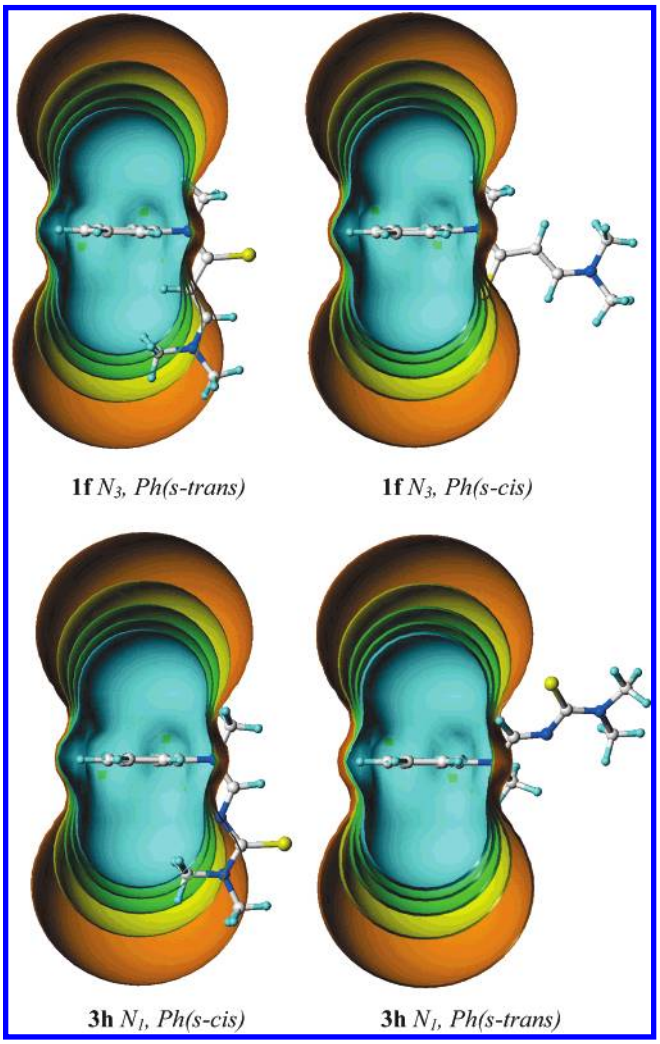

FIGURE 2. Conformers of **1f** and **3h** and calculated ring current effects of the *N*-phenyl rings on H-1, H-2, and N-Me protons (shielding ICSS of −0.1 ppm (orange), −0.2 ppm (yellow), −0.3 ppm (green) and −0.5 ppm (light blue)).

Structural Study of *N,N*-Diaryl-Substituted Thio(seleno)acrylamides. Similarly, in the N(Ph)$_2$-substituted thio(seleno)acrylamides **1e**, **3n**, and **4e**, exchange phenomena due to restricted C_3−N rotation were not observed within the experimental temperature range (vide infra). The ab initio calculations provided global minima structures with completely planar sp^2-hybridized nitrogens of the corresponding N-3 diphenyl substituents (cf. Figure S4, Supporting Information); thus, the corresponding C−N rotation should be restricted in the temperature interval accessed but cannot be so measured due to rotation of the *N*-phenyls. Obviously, concerted dynamic processes, which are still fast on the NMR time scale and which equilibrate ortho and meta protons, are in effect, thereby blocking dynamic effects of the restricted C_3−N rotations which are, in principle, ready for examination. In the case of **1g**, however, with different aromatic moieties (phenyl and naphthyl) on N-3, besides

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TABLE 3. Barriers to Rotation (Solvent, T_c, $\Delta\nu_c$, $\Delta G_c^{\ddagger}$) about the C_1–N Partial Double Bond in Compounds 1–4

compd	solvent	T_c (K)	$\Delta\nu_c$ (Hz)	$\Delta G_c^{\ddagger}$ (kcal/mol)	signal studied
1a	CD_2Cl_2	269	86.54	12.9	$N(Me)_2$
1b	CD_2Cl_2	276	88.56	13.2	$N(Me)_2$
1c	CD_2Cl_2	282	87.56	13.5	$N(Me)_2$
1d	CD_2Cl_2	278	87.71	13.3	$N(Me)_2$
1e	$C_2D_2Cl_4$	306	152.34	14.4	$N(Me)_2$
1f	CD_2Cl_2	290	162.99	13.6	$N(Me)_2$
1g	CD_2Cl_2	207/228	5.11/26.76	14.6	$N(Me)_2$/$N(Me)_2$
2	$C_2D_2Cl_4$	337	129.73	16	$N(Me)_2$
3b	CD_2Cl_2	395	217.34	18.5	$N(Me)_2$
3c	$C_2D_2Cl_4$	398	27.93	20.2	$N(Me)_2$
3d	$C_2D_2Cl_4$	370	22.89	18.9	$N(Me)_2$
3i	$C_2D_2Cl_4$	360	63.99	17.7	$N(CH_2)_2$
3l	$C_2D_2Cl_4$	387	66.62	19	$N(CH_2)_2$
3n	$C_2D_2Cl_4$	386/376	53.66/33.63	19.1/19.0	$O(CH_2)_2$/$N(CH_2)_2$
4b	$C_2D_2Cl_4$	>395	~24.0	>20.2	$N(Me)_2$
4d	$C_2D_2Cl_4$	400	116.69	19.2	$N(Me)_2$
4e	$C_2D_2Cl_4$	>395	~105.1	>19.1	$N(Me)_2$
4f	$C_2D_2Cl_4$	>395	~56.8	>19.5	$N(Me)_2$
4i	$C_2D_2Cl_4$	391	80.86	19.3	$N(CH_2)_2$

the restricted rotation about C_1–N, the restricted rotation about the C_3–N partial double bond could also be examined as the dimethyl group on N-1 group first decoalesces into two singlets (C_1–N rotation) and then further, at still lower temperatures, into four singlets (C_3–N rotation, vide infra). In the global minima of **1e**, **1g**, **3o**, and **4e**, the two aromatic moieties are positioned perpendicular to each other (cf. Figure S4, Supporting Information), but the barrier to the concerted N–C_{ipso} rotations, however, was too low to be measured. The same result was obtained for compound **2**; the global minimum conformer of which is presented in Figure S4 (Supporting Information).

In the case of the N-3 asymmetrically substituted thioacrylamide **1g**, two conformers were also obtained as global minima by ab initio calculations: the cis position of the thiocarbonyl group to phenyl but trans to naphthyl was found to be much more stable (ΔE = 2.45 kcal/mol, see Figure S5 in the Supporting Information). This conformational preference was again verified by GIAO ring current calculations of the two aromatic moieties and evaluating their effects on the chemical shift differences of the N-1 dimethyl group in **1g**: the qualitative agreement of theoretically calculated and experimental values in case of *N_3,naph*(*s-trans*) is in agreement with the aforementioned energy difference of the two conformers and thus implicated this conformer as the anancomer of the conformational system.

Barriers to Rotation about the C–N Partial Double Bonds. In **1**–**4**, one donor and one acceptor substituent are attached to the central C=C or C=N double bonds; thus, due to the push–pull effect, the barrier to rotation about this bond should be lowered, but the lowering was insufficient to enable examination by NMR.[27] However, the corresponding partial double bond character of the bonds of these olefinic carbons to the donor/acceptor substituents are sufficiently high to be studied within the range set by the NMR time scale, and the barrier to rotations were evaluated by DNMR as free energies of activation ($\Delta G_c^{\ddagger}$)[33] at the coalescence temperature (T_c). The T_c values, the chemical shift differences ($\Delta\nu$) of the $N(CH_n)_2$ protons at T_c (by extrapolation from slow exchange) and the corresponding rotation barriers ($\Delta G_c^{\ddagger}$) for the amino-substituted thio(seleno)-acrylamides **1**–**4** are presented in Tables 3 and 4, conditions permitting [barriers to rotation could not be determined in **1f**, **3h**, **3k**, **3m**, **3o**, **4m** and **4f**, this was due to anancomerism (vide supra); in **2e**, **1n** and **4e**, because of concerted rotations of the NPh_2 substituents that are too fast on the NMR time scale (vide supra); in **3o** and **4l**, because of serious signal overlap; and, finally, in **2**, **3l**, **4c** and **4p** due to the rotation barrier being too high to be studied on the NMR time scale (i.e., no exchange phenomena observed at the highest temperatures attained)]. The following points are noted concerning the experimentally determined barriers to rotation:

(i) With respect to the influence on the rotation barrier of the chalcogen elements sulfur and selenium, a number of analogous structures can be compared, e.g., **3c**, **3d**, **3i**, **3l**, **3m**, and **3p** and **4c**, **4d**, **4i**, **4l**, **4m**, and **4p**, respectively. Both barriers to rotation about the C_1–N and C_3–N partial double bonds are higher in the case of C=Se. One reason for this may be the larger polarizability of selenium ($\alpha = 4.56 \times 10^{-30}$ m^3) compared with sulfur ($\alpha = 3.44 \times 10^{-30}$ m^3), as is generally the case with increasing atomic weight along the chalcogen elements,[10,34,35] but negative hyperconjugation was also found to play an important role (vide infra).[15]

(ii) The rotational barriers about the C–N partial double bonds in the amino-substituted thio(seleno)-acrylamides **1**–**4** as a function of the nitrogen substituents follow the order: pyrrolidino > NMe_2 > piperidino > morpholino, thus reflecting the basicity of the corresponding N atoms as provided by reactivity indices.[36,37] The difference in the six-membered rings resulted from the additional –I inductive effect of the oxygen atom in morpholino.[24]

(iii) Because the barrier to rotation about the central HC_1=C_2H partial double bond in push–pull olefins was

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TABLE 4. Barriers to Rotation (solvent, T_c, $\Delta\nu_c$, ΔG) about the C_3–N Partial Double Bond in Compounds 1–4

compd	solvent	T_c (K)	$\Delta\nu_c$ (Hz)	$\Delta G_c^{\ddagger}$ (kcal/mol)	signal studied
1a	CD_2Cl_2	277	180.63	12.9	$N(CH_2)_2$
1b	CD_2Cl_2	296	86.8	14.2	$N(Me)_2$
1c	CD_2Cl_2	263	200.43	12.1	$N(CH_2)_2$
1d	$C_2D_2Cl_4$	372/356	121.05/38.05	17.8/17.8	$N(CH_2)_2/(CH_2)_2$
1g	$C_2D_2Cl_4$	312	158.52	11.0/11.4	$N(Me)_2$
3b	CD_2Cl_2	398	48.9	19.8	$N(Me)_2$
3c	$C_2D_2Cl_4$	356/376	24.46/68.55	18.1/18.4	O(CH2)2/$N(CH_2)_2$
3d	$C_2D_2Cl_4$	384	36.96	19.3	$N(CH_2)_2$
3h	$C_2D_2Cl_4$	395	41.07	19.8	$N(Me)_2$
3i	$C_2D_2Cl_4$	374	55.81	18.5	$N(Me)_2$
3k	$C_2D_2Cl_4$	350/364	21.57/61.38	17.9/17.9	$O(CH_2)_2/N(CH_2)_2$
3m	$C_2D_2Cl_4$	>395	~25.7	>20.2	$N(CH_2)_2$
3p	$C_2D_2Cl_4$	388	80.63	18.9	$N(CH_2)_2$
4b	$C_2D_2Cl_4$	>395	~88.8	>19.2	$N(Me)_2$
4c	$C_2D_2Cl_4$	396	111.7	19.1	$N(CH_2)_2$
4d	$C_2D_2Cl_4$	>395	~68.5	>19.4	$N(CH_2)_2$
4i	$C_2D_2Cl_4$	>395	~93.7	>19.1	$N(Me)_2$
4m	$C_2D_2Cl_4$	≫395	~62.2	≫19.5	$N(CH_2)_2$
4p	$C_2D_2Cl_4$	>395	~123.0	>18.9	$N(CH_2)_2$

previously found to be 2–3 kcal/mol higher than the HC_1=N analogues,[43] the corresponding C_1–N and C_3–N barriers **1** and **2** compared with **3** and **4** were found to be 5–6 kcal higher in the latter compounds due to the greater "vinylogous thioamide resonance".

However, the conclusions to be drawn from these experimental results are somewhat limited. In many cases, the barriers could not be measured on the NMR time scale for various reasons, thus leaving only a limited number of cases experimentally accessible. In addition, the relative energies of both the ground states (GS) and the transition states (TS) of the rotations about the C–N partial double bonds are not available, only the difference of the two are, but both are characteristically contributing to the electron delocalization. For this reason, the global minimum energies and structures of both the GS and TS of the dynamic processes in **1**–**4** were determined by theoretical calculations at the ab initio level of theory.

Theoretical Calculation of the Barriers to Rotation About the C_1–N and C_3–N Partial Double Bonds in Amino-Substituted Thio(seleno)acrylamides 1–4. In the GS, the substituents on N-1 and N-3 are in the plane of the molecule and the global minimum results from the lowest steric hindrance. In the TS, the $N(1)R_2$ and $N(3)R'_2$ moieties are at an angle of 90°, respectively [i.e., the planes of the two substituents NR_2 and NR'_2—the nitrogens are sp^3-hybridized—are at an angle of 90° to the planes of the HC_1=$C_2H(N)C_3$=$S(Se)NR'_2$ and R_2N–C_1H=$C_2H(N)C_3$=S(Se) segments, respectively]. The characteristic feature that is most distinctive between the geometries of the two states is the length of the HC_1–N and C_3–N partial double bonds, which are truly single bonds in the TS (see Table S3, Supporting Information). Thus, it is necessary, indeed crucial, to calculate accurate structures for the TS of the compounds **1**–**4** for further and more detailed information concerning their dynamic behavior. The various TS were developed by the TRIPOS force field and energy optimized using the semiempirical PM3 method; the structures, thus obtained (and also the corresponding GS found by the same procedure), were employed as starting structures for geometry optimization at the ab initio level of theory (HF/6-31G*, HF/6-311G**, SCIPCM-HF/6-31G*, and B3LYP/6-31G*). As an example, in Figure 3, the TS of the restricted rotations about the C_1–N and C_3–N partial double bonds of **1b** are depicted [two TS were obtained having the lone pair of the now sp^3-hybridized nitrogen in cis and trans positions to C^1=$C^2(N^2)$] and in Table S4 (Supporting Information) both the corresponding GS and TS energies and barriers to C–N rotation as obtained at the various levels of theory are given.

The barriers calculated at the semiempirical PM3 level were far too low (due to unavailable parameters for selenium, compounds **2** and **4** could not even be calculated), and the relative differences between C_1–N and C_3–N were not reproduced. The higher barriers in **3** compared with **1**, on the other hand, were correctly found, but otherwise did not correspond well. The calculational results improved at the ab initio level of theory [for two TS (cf. Figure 3 and Table S4 in Supporting Information), only the more stable with the nitrogen lone pairs trans to C^1=$C^2(N^2)$ was considered further], though the calculated rotation barriers were still too low. In addition, characteristic structural influences on the two barriers (C=S versus C=Se, NR_2 variation and HC_1=C_2H versus HC_1=N_2) are tenuously correctly reproduced. Due to these shortcomings, additional calculations were performed either where the basis set was extended to HF/6-311G**, the solvent (CD_2Cl_2) was included (SCIPCM-HF/6-31G*) in the calculations or DFT calculations (B3LYP/6-31G*) were performed (see Table S4, Supporting Information). Both the extended triple-ζ-split-valence basis set, which better represents sulfur and selenium by employing polarization functions, and the inclusion of the solvent into the calculations improved the agreement of the calculated rotation barriers with those measured experimentally (cf. Table S4 and Table S5,

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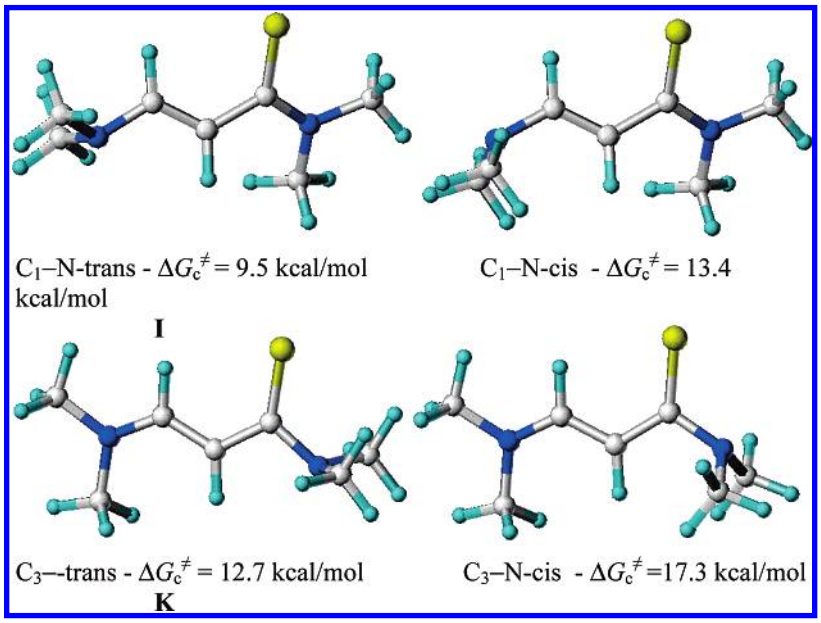


FIGURE 3. Transition states of the restricted rotations about the C^1–N (**I**) and C^3–N (**K**) partial double bonds of the amino-substituted thioacrylamide **1b** (cis and trans saddle point rotamers of C^1–N and C^3–N shown).

Supporting Information). The best results were obtained employing the double-ζ-split-valence basis set and considering the solvent-SCIPCM[44] (at the HF/6-31G* level of theory, $R^2 = 0.8356$ for C_1–N and $R^2 = 0.7766$ for C_3–N; at the SCIPCM-HF/6-31G* level of theory, $R^2 = 0.8126$ for C_1–N and $R^2 = 0.8746$ for C_3–N; cf. Figure S6 and Table S6, Supporting Information). For the DFT results, the calculated rotation barriers further approach the experimental values, and obviously electron correlation which is included in these calculations improves the representation of the electronic situation (at the B3LYP/6-31G* level of theory, $R^2 = 0.8534$ for C_1–N and $R^2 = 0.8799$ for C_3–N; cf. Figure S6 and Table S6, Supporting Information). The theoretical calculations help filling in the voids in the experimental rotational barriers (Tables 3 and 4) and complete sets of barriers to rotation about the two C–N partial double bonds are thus available. In addition to conclusions (i)–(iii), which were all confirmed, the following additional points are worth noting:

(iv) For the amino-substituted selenoacrylamide **2**, exchange phenomena for the C_3–N substituent were not obtained within the temperature range available (cf. Table 4). The calculated barrier to C_3–N rotation, only 4.7 kcal/mol, corroborates this experimental finding and thus the rotation barrier is too low to be studied on the NMR time scale.

(v) The relative size of the two barriers to rotation in **1g** are now comparable: the rotation barrier about C_1–N (experimental, 14.6; calculated, 13.3 kcal/mol) proved to be larger than the rotation barrier about C_3–N (experimental, 11.4 kcal/mol; calculated, 10.5 kcal/mol).

(vi) In the case of the amino-substituted selenoacrylamides **4**, only the C_1–N barriers of **4d**, **i** and the C_3–N barrier of **4c** could be experimentally obtained (cf. Tables 3 and 4); the other corresponding barriers proved to be too high to be studied by DNMR. This experimental result is explicitly corroborated by the present calculations; barriers to rotation above 19 kcal/mol were calculated. The entire sets of amino-substituted thioacrylamides **3** and amino-substituted selenoacrylamides **4** can now be compared with respect to the influence on the barrier of the chalcogen element, however, the larger barriers in the case of selenium cannot be fully substantiated by the ab initio calculations as the actual differences were calculated to be only negligible.

(vii) The rotation barrier for the C_1–N and C_3–N partial double bonds in the case of N(Me)Ph substituents could not be studied for several reasons (vide supra). The barriers as calculated are very similar to the *N*-dialkyl analogues, corroborating the former observation that the aryl twist is dramatic, ca. 90°, completely preventing aromatic resonance influence on the barriers to rotation.

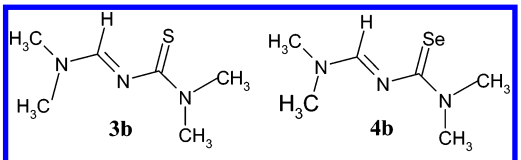
(viii) In the case of **3l** and **3m** (for N-3, R_2 = pyrrolidino), the C_3–N barrier to rotation could not be obtained (cf. Table 4) and this in complete agreement with the ab initio result, calculated as being in excess of 22 kcal/mol. The same is true for the C_1–N barriers of **3k** and **3o**.

To further theoretically understand the structural influences (i)–(viii) on the two C–N barriers to rotation and to draw firmer conclusions regarding these influences in terms of "resonance" along the amino-substituted thio(seleno)acrylamides, the compounds were further studied by NBO analysis.[40]

NBO Analysis of Amino-Substituted Thio(seleno)-acrylamides 1–4. At the HF/6-31G* level of theory, the occupation of the various molecular orbitals of both bonding electron pairs and lone electron pairs in the compounds were assessed and the structural differences compared accordingly. These occupancies are provided in Table S3 (Supporting Information). If the compounds are compared with respect to "resonance" determining the two barriers to rotation about the C–N bonds, the following molecular orbital interactions are revealed as the most significant: (i) the lone pair of N-1 with the antibonding π^* orbital of the central partial C_1=C_2 (C_1=

(44) (a) Hartmann, H.; Heyde, C.; Zug, I. *Synthesis* **2000**, 805. (b) Noack, A.; Hartmann, H. *Tetrahedron* **2002**, *58*, 2137. (c) Zug, I.; Hartmann, H. *Z. Naturforsch.* **2002**, *57b*, 420.

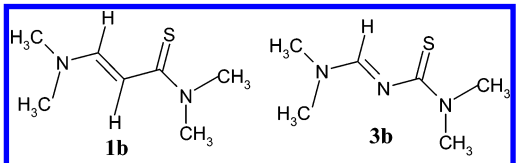
SCHEME 8[a]



	3b		**4b**
	20.3 [a]/19.8 [b] 20.7 [c]/19.5 [d]		>20.2 [a]/>19.4 [b] 20.9 [c]/19.0 [d]
lone pair N-1 [e]	1.68920	lone pair N-1	1.68899
$\pi^*_{C^1=N^2}$ [e]	0.25783	$\pi^*_{C^1=N^2}$	0.25991
$\pi_{C^1=N^2}$ [e]	1.85631	$\pi_{C^1=N^2}$	1.85556
$p_{N^1\text{-}C^1}$ [f]	1.327	$p_{N^1\text{-}C^1}$	1.326
$p_{C^1=N^2}$ [f]	1.285	$p_{C^1=N^2}$ [f]	1.286
lone pair N-3 [e]	1.67038	Lone pair N-3	1.65396
$p_{N^2\text{-}C^3}$ [f]	1.373	$p_{N^2\text{-}C^3}$	1.369
p_{C^3,N^3} [f]	1.333	p_{C^3,N^3}	1.326

[a] Key: (a) C^1−N barrier; (b) C^3−N barrier; (c) C^1−N barrier, as calculated; (d) C^3−N barrier, as calculated; (e) orbital occupation number; (f) bond length.

SCHEME 9[a]



	1b		**3b**
	13.2 [a]/14.2 [b] 12.3 [c]/12.7 [d]		20.3 [a]/19.8 [b] 20.7 [c]/19.5 [d]
lone pair N-1 [e]	1.73049	lone pair N-1	1.68920
$\pi_{C^1=C^2}$ [e]	1.85463	$\pi_{C^1=N^2}$	1.85431
$\pi^*_{C^1=C^2}$ [e]	0.20551	$\pi^*_{C^1=N^2}$	0.25783
$\pi^*_{C=S}$ [e]	0.42210	$\pi^*_{C=S}$	0.44294
$p_{N\text{-}C^1}$ [f]	1.344	$p_{N\text{-}C^1}$	1.327
$p_{C^2\text{-}C^3}$ [f]	1.455	$p_{N^2\text{-}C^3}$	1.373
lone pair N-3 [e]	1.68527	lone pair N-3	1.67038
p_{C^3,N^3} [f]	1.341	p_{C^3,N^3}	1.333
$p_{C=S}$ [f]	1.698	$p_{C=S}$	1.706

[a] Key: (a) C^1−N barrier; (b) C^3−N barrier; (c) C^1−N barrier, as calculated; (d) C^3−N barrier, as calculated; (e) orbital occupation number; (f) bond length.

N_2) double bond and also the π orbital of the C_1=C_2 bond with the antibonding π^* orbital of the C=S(Se) bonds for the C_1−N barrier and (ii) the lone pair of N-3 with the π^* orbital of the C=S(Se) bonds for the C_3−N barrier (cf. Scheme 3). These molecular interactions and the occupancies of the corresponding orbitals were employed to quantify the "resonance" as the source for the rotation barriers and have been compared with respect to structural variations (i)−(iii) in the thio(seleno)acrylamides **1**−**4**. In respect to this, the comparison of thio (**3**) and seleno analogues (**4**) (cf. Scheme 8), of olefino (**1**) and imino analogues (**3**) (cf. Scheme 9), as well as the structural variations due to the NR_2 substituents (cf. Scheme 10) proved most illuminating:

(i) Replacement of sulfur by selenium increases the two C−N barriers to rotation (vide supra); accordingly, the occupations of the two nitrogen lone pairs are reduced, the occupation of the $\pi^*_{C(1)=N(2)}$ orbital raised and that of the $\pi_{C(1)=N(2)}$ orbital reduced. The corresponding bond length variations C_1−N_1, N_2−C_3, and C_3−N_3 are shortened, whereas C_1=N_2 is lengthened.

(ii) The same is true when comparing the corresponding **1** and **3** analogues. Replacement of C_1=C_2 by C_1=N_2

SCHEME 10[a]

Me_2N-CH=CH-C(S)-NR'_2

NR'_2		C^3,N [a]	N^3-lone pair [b]	$\pi^*_{C=S}$ [b]	$p_{C^3,N}$ [c]	$p_{C=S}$ [c]
	**1d**	17.8	1.67966	0.42559	1.334	1.699
-NMe_2	**1b**	14.2	1.68527	0.42210	1.341	1.698
	**1a**	12.9	1.68992	0.40899	1.343	1.700
	**1c**	12.1	1.68826	0.41468	1.344	1.700

[a]C^3,N barrier to rotation. [b]Orbital occupation number. [c]Bond length.

[a] Key: (a) C^3,N barrier to rotation; (b) orbital occupation number; (c) bond length.

increases the two barriers to C−N rotation dramatically (vide supra); accordingly, the occupations of the two nitrogen lone pairs are strongly reduced, the occupation of the $\pi^*_{C(1),C(2)(N-2)}$ orbital and the $\pi^*_{C=S}$ raised and that of the $\pi_{C(1),C(2)(N-2)}$ orbital reduced. The corresponding bond length variations are: C_1−N_1, $C_2(N_2)$−C_3, and C_3−N are shortened, whereas C=S is lengthened.

(iii) Finally, the effect of the NR_2 substituents on the C−N barriers to rotation and "resonance", respectively, is correctly reproduced: in line with the C_3−N barrier decrease the occupation of $\pi^*_{C=S}$ also decreases while the occupation of the N-3 lone pair increases. The corresponding bond length change, C_3−N shortens (C=S remains almost constant), corroborates the corresponding "resonance" along the present system.

From this NBO study, not even the slightest hint was obtained that the dynamic behavior of the amino-substituted thio(seleno)acrylamides **1**−**4** could not be discussed within the traditional thio(seleno)amide (vinylogous) "resonance" concept. However, the previous statement[25] that approximately the same amount of thioamide/vinylogous thioamide resonance is in effect cannot hold because C_3−N/C=S(Se) proved to be stronger than C_1−N/C=S(Se) resonance via C_1=C_2(N), however, the difference is simply balanced by the N-1 lone pair/$\pi^*_{C(1)}$=$_{C(2)(N-2)}$ resonance (cf. Schemes 8−10 and Table S3, Supporting Information).

Anisotropic Effect of the C=S and C=Se Groups. In addition to the ring current effect of *N*-phenyl (for differentiating the conformers with respect to C_1−N and C_3−N restricted rotation), the anisotropic effects of the thiocarbonyl and the selenocarbonyl groups were also calculated by the same method.[32] The two effects, visualized in Figure 4, proved to be rather similar and not too far reaching (ICSS for ±0.1 ppm at ca. 5 Å). This is about the same, in distance terms, as that available from NOE measurements used for stereochemical determinations. However, because for distances <3.5 Å the calculated anisotropic effects are not very reliable,[27,32] this approach is therefore not very useful for stereochemical applications when comparing thiocarbonyl and the selenocarbonyl. This is in contrast to the case where carbonyl anisotropy was compared with thione[32,41] and could be successfully employed for assignments in ^{1}H NMR spectroscopy.[42,43] Thus, as the differences are only marginal when comparing C=S with C=Se, the consequences for correct assignment in ^{1}H NMR[35] are obvious.

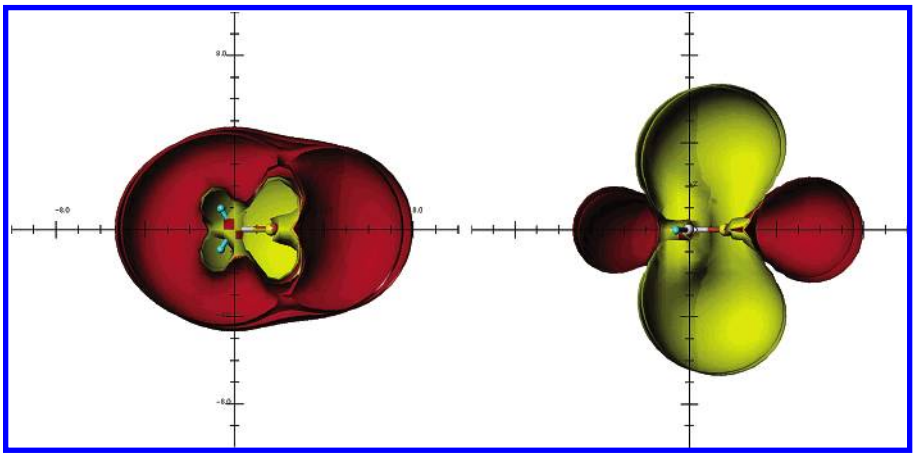


FIGURE 4. Anisotropic effects of thiocarbonyl (inner ICSS) and selenocarbonyl groups (outer ICSS) in thioformaldehyde and selenoformaldehyde as calculated by NICS analysis (shielding surfaces at 0.1 ppm in yellow; deshielding surfaces at 0.1 ppm in red). View from perpendicular to the molecules (left) and in the plane of the molecules (right).

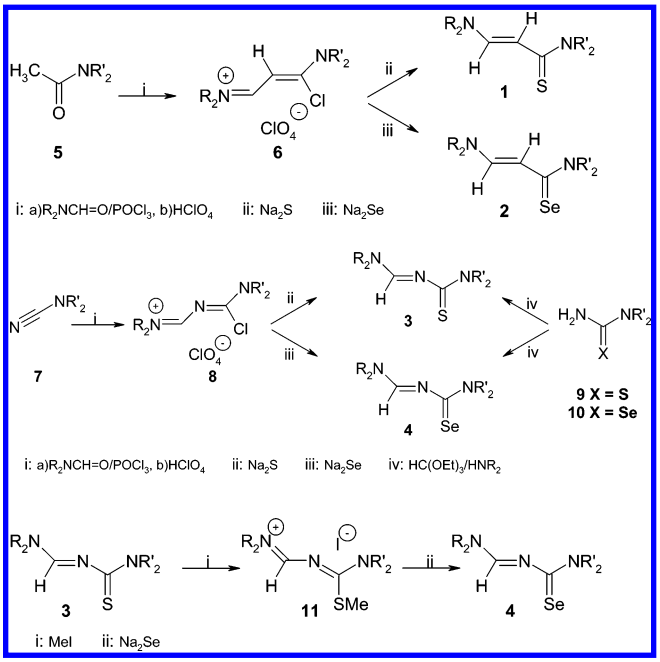
Conclusions

A series of amino-substituted thio(seleno)acrylamides **1**−**4** was synthesized and studied with respect to π electron distribution. The compounds exist as preferred *E(s-cis)* isomers; when N(Me)Ph substituents are present, further preferred conformations [*N_3,Ph(s-trans)* and *N_1,Ph(s-trans)* to C=S(Se)] were observed. Of the various methodologies applied for the assignment procedure, the application of the GIAO ab initio-calculated ring current effect of *N*-phenyl was found to be extremely useful.

The restricted rotations about the C_1−N and C_3−N partial double bonds were studied by experimentally DNMR spectroscopy, the barriers to rotation ($\Delta G_c^{\ddagger}$) determined and discussed with respect to structure: $\Delta G_c^{\ddagger}$ values in the amino-substituted selenoacrylamides **2** and **4** are larger than in thio analogues **1** and **3** due to the higher polarizability of selenium; $\Delta G_c^{\ddagger}$ in **1** are 3−5 kcal/mol smaller than in imino analogues **3** due to the higher bond order of C_1=C_2 compared with C_1=N_2 and the corresponding lower "vinylogous resonance"; finally, the barrier dependence on NR_2 substitution for $\Delta G_c^{\ddagger}$ proved to be: pyrrolidino > NMe_2 > piperidino > morpholino. In addition, further conclusions were obtained after calculating the C−N barriers to rotation at the ab initio level of theory: experimentally inaccessible rotation barriers (too low in the case of **2** and too high in the case of **4**) or not assessable by NMR due to heavily biased conformations [in the case of N-1(N-3) methyl phenyl] or concerted mechanisms (in the case of N-3 diaryl) are now theoretically available and can be discussed within the context of structure.

By means of the NBO analysis of **1**−**4**, the occupation numbers of the lone electron pairs of N-1/N-3, of the bonding/antibonding π/π^* orbitals of the central C_1=C_2/C_1=N_2 partial double bonds and of the antibonding π^* orbitals of the C=S(Se) bonds were calculated and shown to quantitatively describe thio(seleno)amide/vinylogous thio(seleno)amide "resonance". Thus, similar $\Delta G_c^{\ddagger}$ values for C_1−N and C_3−N restricted rotations do not indicate the same amount of the two "resonance interactions" as thio(seleno)amide resonance proved to be much stronger. However, the difference to the "vinylogous resonance" is balanced by additional N-1 lone pair/$\pi^*_{(C1,C2/N2)}$ orbital interactions.

SCHEME 11



The thiocarbonyl and the selenocarbonyl anisotropic effects were quantitatively calculated by the GIAO method and visualized by ICSS. They proved to be very similar with ±0.01 ppm isochemical shielding surfaces running at about the same distances from the respective nuclei. This equidistance of C=S and C=Se anisotropic effects ought to be considered if the effects are to be employed for assignment purposes in ^{1}H NMR spectroscopy when comparing C=S and C=Se analogues.

Experimental Section

The compounds studied were synthesized according to reported methods (cf. Scheme 11). Thus, amino-substituted thioacrylamides **1** and their seleno analogues **2** were prepared[44] by the reaction of sodium sulfide or sodium selenide, respectively, with 1-chlorovinamidinium salts **6** which were available by reaction of acetamides **5** with Vilsmeier reagent[45]

(45) Jones, G.; Stanforth, S. P. *Org. React.* **1997**, *49*, 1 and references therein.

prepared from *N*,*N*-disubstituted formamides and $POCl_3$.[46] For the synthesis of the analogous aza thioacrylamides **3** and selenoacrylamides **4**, two different routes were used. The first route (method A) started with *N*,*N*-disubstituted cyanamides **7**[47] which were transformed by reaction with Vilsmeier reagent into the 1-chlor-2-azavinamidinium salts **8**,[48] their subsequent reaction with sodium sulfide or sodium selenide gave rise to the formation of the desired products **3** and **4**, respectively. In an alternative route (method B), the same compounds **3** and **4** were prepared by reaction of *N*,*N*-disubstituted thioureas **9**[49] or selenoureas **10**,[50] respectively, with a mixture of triethyl orthoformate and a secondary amine according to ref 51. The sodium selenide reagent required was prepared by the reaction of sodium borohydride and selenium in methanol.[52] In a few cases, the analogous aza selenoacrylamides **4** were synthesized by the reaction of sodium selenide with 1-methylmercapto-2-azavinamidinium iodides which were prepared from the amino-substituted 2-azathioacrylamides **3** by reaction with methyl iodide (method A1). The preparative results **1**−**4** (method of synthesis, yirlds, melting points, elemental analyses) and general procedures are given in the Supporting Information.

The ^1H and ^{13}C NMR spectra were acquired at 11.75 (operating at 500 and 125 MHz for ^1H and ^{13}C, respectively) and 7.05 T (operating at 300 and 75 MHz for ^1H and ^{13}C, respectively) at room temperature in CD_2Cl_2 except for the DNMR experiments where both higher and lower temperatures were used (in the case of higher temperatures, $C_2D_2Cl_4$ was substituted for CD_2Cl_2 as the solvent). Determination of the actual probe temperature was made using standard NMR thermometers. ^{13}C NMR spectra were acquired using a 10 s repetition time with proton broadband decoupling. All ^1H and ^{13}C chemical shifts were referenced using TMS as an internal standard (= 0 ppm for both nuclei). NMR spectra were assigned by the application of APT and 2-D techniques such as HMQC, HMQC-TOCSY and HMBC using standard vendor-supplied software.

The free energies of activation were calculated by means of eqs 1 and 2:

$$k_c = \frac{\pi \Delta \nu}{\sqrt{2}} \tag{1}$$

$$\Delta G_c^{\ddagger} = 19.14 T_c \left[10.32 + \log\left(\frac{T_c}{k_c}\right) \right] \tag{2}$$

Quantum chemical calculations were performed on SGI Octane R12000 and SGI Origin workstations using the Gaussian 98 software package. The molecules were optimized at different levels of theory using the keyword opt, optimization of transition states of the rotation about the C_1−N and C_3−N partial double bonds using opt = ts and calcfc. The NBO 5.0 population analysis[53] was used linked to the Gaussian 98 program package[54] with the keywords nlmo for NLMO analysis and print for graphical evaluation. NRT analysis was performed within the NBO 5.0 population analysis with nrt and nrtthr = 10. The results were illustrated using the program SYBYL.[55]

The chemical shieldings in the surroundings of the molecules were calculated as described in ref 32. Within the SYBYL contour file, the anisotropy/ring current effects of the functional groups under investigation were visualized as ICSS enabling appreciation of the spatial extension of the anisotropy/ring current effects to particular protons.

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Supporting Information Available: General procedures for the synthesis of the compounds under study; tables of experimental ^1H and ^{13}C chemical shifts; tables of the results from NBO analysis and ab initio calculations for the geometries and energies of both ground and transition states for the restricted rotations about the C_1−N and C_3−N partial double bonds; figures of isomers and conformers; and correlations of experimental values with theoretically calculated C,N rotation barriers. This material is available free of charge via the Internet at http://pubs.acs.org.

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