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Data Article

Fragmentation of 1,4,2-oxaselenazoles as a route to isoselenocyanates–A high-level CBS-QB3 study

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ABSTRACT

In this study, the thermodynamics and barrier heights associated with the fragmentation reactions of a set of fifteen 1,4,2-oxaselenazoles into isoselenocyanates (molecules with promising anticancer activity) and carbonyl derivatives, have been studied using the high-level CBS-QB3 quantum chemical protocol. Of the systems studied, attachment of a CF_3-substituent at the C5-position affords the system with the largest gas-phase free energy barrier (190.1 kJ mol^{-1}), whilst substitution at the C5-position with two $-NMe_2$ substituents affords a heterocycle with the lowest free energy barrier (67.8 kJ mol^{-1}). The presence of solvent (acetonitrile) was shown to reduce the free energy barriers in all cases, with the two systems mentioned above having condensed-phase free energy barriers of 180.8 and 42.0 kJ mol^{-1}, respectively.

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Specifications Table

Subject area	*Organic Chemistry*
Compounds	*1,4,2-oxaselenazoles, isoselenocyanates, carbonyl derivatives*
Data category	*High-level quantum chemical values*
Data acquisition format	*Quantum chemical calculations*
Data type	*Thermodynamic and kinetic data*
Procedure	*CBS-QB3 composite protocol*
Data accessibility	*Included in article, with geometries of all species included in the Supporting Information*

1. Rationale

Isoselenocyanates (ISCs), molecules containing the -N=C=Se functionality, are gaining increased attention because of their potent anticancer activity. For example, numerous ISCs have shown promising results in the possible prevention and treatment of melanoma. [1,2] Concerning colon cancer, 4-phenylbutyl ISC (4-ISC) has been shown to reduce colon tumor growth in naked mouse models, [3] and has also shown a synergistic effect with cetuximab for the treatment of 5-fluorouracil-resistant colon cancer. [4] In addition, 4-ISC has been shown to modulate phase I and II enzymes and inhibit 4-(methylnitrosamino)−1-(3-pyridyl)−1-butanone-induced DNA adducts in mice. [5] The ISC analogue of sulforaphane (an isothiocyanate with well-studied anticancer activity) has been shown to be more effective in killing HepG2 cancer cells, yet was less toxic to non-cancer mouse embryonic fibroblast (MEF) cells, than sulforaphane. [6] In addition, organofluorine isoselenocyanate analogues of sulforaphane demonstrated higher anticancer activity against two breast cancer cell lines compared with sulforaphane, and were also shown to be less toxic to healthy cells than the latter. [7]

Despite these especially promising results, only a very small number of ISCs have been subjected to biological evaluation, and therefore, the effect of substituents in governing the biological properties of ISCs has not yet been thoroughly surveyed. In this light, development of libraries of ISCs that may be screened with the intention of identifying those with the highest efficacy would be highly desirable. The development of large and structurally diverse libraries of such compounds ideally requires efficient synthetic methods by which they may be prepared. One attractive (but relatively unstudied) route by which ISCs may be prepared is via the thermally induced fragmentation reactions of 1,4,2-oxaselenazoles (Scheme 1). [8,9] One particularly attractive feature of this route for preparing ISCs is that it is potentially suited to the development of a polymer-supported synthesis of such compounds. This is especially plausible given that a polymer-supported synthesis of isothiocyanates, based on the fragmentation of polymer-bound 1,4,2-oxathiazoles (i.e., where Se is replaced with S in the heterocyclic ring system) has already been reported. [10,11]

Knowledge of how substituents affect the magnitude of the thermodynamics and kinetics of such fragmentation reactions would be immensely valuable in selecting appropriate 1,4,2-oxaselenazole frameworks that could be used to provide ISCs in the most efficient manner (e.g., those that afford ISCs with low activation energies, thereby reducing the temperatures required to induce fragmentation, which might otherwise result in thermal degradation of the polymer support). This present study employs the high-level CBS-QB3 protocol [12] to study the effect of substituents at the C5-position, which is where attachment of the heterocyclic moiety to the solid support would occur, on the energetics associated with the fragmentation of 1,4,2-oxaselenazoles. The present study does not include a consideration of the effect of the migrating group at the C3-position on the fragmentation

Scheme 1. Fragmentation of 1,4,2-oxaselenazoles to afford isoselenocyanates.

Table 1
Effect of substituents on the thermodynamics and barriers associated with fragmentation of 1,4,2-oxaselenazole derivatives into carbonyl and isoselenocyanate products ($R^1 = CH_3$ in all cases, and energies reported in kJ mol^{-1}).

System	R^2	R^3	$\Delta H^{o}_{(gas)}$	$\Delta G^{o}_{(gas)}$	$\Delta G^{o}_{(MeCN)}$	$\Delta H^{o,\ddagger}_{(gas)}$	$\Delta G^{o,\ddagger}_{(gas)}$	$\Delta G^{o,\ddagger}_{(MeCN)}$
1	H	CF_3	−25.4	−96.3	−103.0	197.7	190.1	180.8
2	H	H	−42.4	−109.0	−114.4	187.7	179.4	169.7
3	H	CN	−40.5	−108.9	−112.5	185.9	177.9	173.8
4	H	PMe_2	−39.5	−110.6	−117.5	181.5	173.2	163.9
5	H	CHO	−37.9	−104.6	−109.2	180.7	174.4	165.8
6	H	Me	−52.9	−122.1	−133.5	176.1	164.0	149.0
7	CN	CN	−46.2	−114.7	−114.9	174.8	167.8	163.8
8	Me	Me	−58.5	−132.1	−147.2	169.4	155.8	134.5
9	H	Ph	−63.4	−130.1	−139.6	161.5	153.1	138.7
10	H	SMe	−81.3	−149.0	−150.1	149.3	137.7	127.7
11	H	OMe	−108.6	−178.7	−186.6	130.4	115.9	100.9
12	CF_3	NMe_2	−98.7	−173.6	−188.0	122.9	113.5	97.6
13	H	NMe_2	−111.2	−181.5	−195.3	104.3	93.1	76.2
14	CN	NMe_2	−118.4	−189.2	−204.3	103.0	94.6	79.9
15	NMe_2	NMe_2	−123.3	−198.0	−221.4	82.7	67.8	42.0

barriers, as on the basis of previous studies pertaining to the fragmentation reactions of 1,4,2-oxathiazole derivatives, such effects are expected to be relatively small in magnitude. [10,11,22] The results of this study are expected to be of great utility in potentially guiding the development of an efficient polymer-supported approach for obtaining ISCs.

2. Procedure

The structures of all species were optimized at the B3LYP/6–31G(2df,p) level of theory, and were confirmed as equilibrium or transition states through inspection of the number of imaginary frequencies, with the former being characterized by having all real frequencies, and the latter having a single imaginary frequency. To confirm the validity of all transition structures as those linking the reactant heterocycles with the corresponding isoselenocyanate and carbonyl products, intrinsic reaction coordinate (IRC) calculations were performed in both the forward and reverse directions. Having obtained optimized structures for all species, the reaction enthalpies (ΔH^{o}) and enthalpies of activation ($\Delta H^{o,\ddagger}$) at 298 K (as well as the corresponding free energies (ΔG^{o}) and free energy barriers ($\Delta G^{o,\ddagger}$) were obtained by way of high-level CBS-QB3 calculations (which have been modified slightly in the sense that B3LYP/6–31G(2df,p) geometries have been employed, rather than the prescribed B3LYP/6–311G(2d,d,p) geometries as employed in the original CBS-QB3 procedure). [12] It should be pointed out that the CBS-QB3 protocol has been shown previously to afford reliable thermochemical [13] and barrier height [14] data (relative to benchmark-quality W1w values, i.e., all-electron CCSD(T) energies at the complete-basis-set limit) for the fragmentation reactions of the closely-related 1,4,2-dioxazole and 1,4,2-oxathiazole derivatives (which afford isocyanates and isothiocyanates, respectively). The zero-point vibrational energies (ZPVEs), thermal corrections to enthalpy (H_{vib}) and entropy corrections (S_{vib}) have been scaled according to factors found in the literature, namely: 0.9861, 0.9909, and 0.9946, respectively. [15] All calculations have been performed using the Gaussian 09 program package (Revision D.01). [16]

3. Data, value and validation

In this study the effect of the nature of the substituents at the C5-position (i.e., R^2 and R^3, Scheme 1), on both the fragmentation thermodynamics and barrier heights, have been investigated. In this light, Table 1 contains: (i) the enthalpies ($\Delta H^{o}_{(gas)}$) and enthalpic barriers ($\Delta H^{o,\ddagger}_{(gas)}$), and (ii) the free energies ($\Delta G^{o}_{(gas)}$) and free energy barriers ($\Delta G^{o,\ddagger}_{(gas)}$), which have been obtained using the composite CBS-QB3 protocol (at 298 K). From the perspective of reaction mechanism, all of the fragmentations

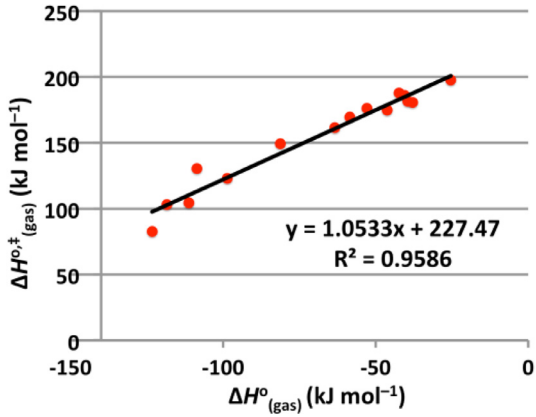

Fig. 1. Bell-Evans-Polanyi plot for the fragmentation reactions of 1,4,2-oxaselenazoles.

considered in this study are concerted in nature (in which the migration of the methyl group occurs in concert with cleavage of the C(5)–Se and O–N bonds). The geometries (obtained at the B3LYP/6–31G(2df,p) level of theory) of all reactant, transition state, and product species are provided in the Supporting Information. In addition, the effect of solvent (acetonitrile), has been considered in a qualitative manner by adding free energy of solvation corrections (obtained at the SMD/M05-2X/6–31G(d) level of theory) [17,18] to the underlying gas-phase free energies (giving $\Delta G^{o}_{(MeCN)}$) and free energy barriers (giving $\Delta G^{o,\ddagger}_{(MeCN)}$).

Beginning with a consideration of the gas-phase results, for this set of 1,4,2-oxaselenazole fragmentations, a Bell-Evans-Polanyi relationship [19,20,21] is observed. In this context, a linear plot of the enthalpy of activation ($\Delta H^{o,\ddagger}_{(gas)}$) versus the enthalpy of fragmentation ($\Delta H^{o}_{(gas)}$) exists, with an R^2 value of 0.9586 (Fig. 1). In particular, system **1** ($R^2 = H$, $R^3 = CF_3$) is associated with the highest barrier ($\Delta H^{o,\ddagger}_{(gas)} = 197.7$ kJ mol^{-1}) and least exothermicity ($\Delta H^{o}_{(gas)} = -25.4$ kJ mol^{-1}). In contrast, system **15** ($R^2 = R^3 = NMe_2$) fragments with the lowest enthalpic barrier ($\Delta H^{o,\ddagger}_{(gas)} = 82.7$ kJ mol^{-1}) and with the greatest exothermicity ($\Delta H^{o}_{(gas)} = -123.3$ kJ mol^{-1}). Given the dissociative nature of these reactions, the free energies of fragmentation are always more negative (by amounts ranging from 66.6 to 74.9 kJ mol^{-1}), while the free energies of activation are also smaller than the corresponding enthalpies of activation (by amounts ranging from 6.3 to 14.9 kJ mol^{-1}). In this regard, system **15** fragments with an especially low free energy barrier of just 67.8 kJ mol^{-1}, whilst system **1**, which is the least easily fragmented structure has a $\Delta G^{o,\ddagger}_{(gas)}$ value of 190.1 kJ mol^{-1}.

Other notable findings to emerge from this data set include: (i) the attachment of a phenyl substituent (as in system **9**) results in only a relatively small decrease in the fragmentation free energy barrier compared with the parent unsubstituted system **2** ($\Delta G^{o,\ddagger}_{(gas)} = 153.1$ vs 179.4 kJ mol^{-1}), (ii) in considering the effect of the presence of an electron-donating dimethylamino (as in system **13**) versus methoxy substituent (as in system **11**), the data indicates that the amino group provides a lower free energy barrier to fragmentation (by 22.8 kJ mol^{-1}) compared with the methoxy substituent, (iii) in comparing the effect of an –OMe versus –SMe substituent, the former affords a heterocyclic system with a notably lower free energy barrier (by 21.8 kJ mol^{-1}), (iv) the presence of a $-PMe_2$ substituent affords a heterocycle (system **4**) that fragments with a significantly higher free energy barrier (by 80.1 kJ mol^{-1}) than that substituted with $-NMe_2$ (system **13**), and (v) of all of the substituents considered, only the $-CF_3$ group affords a system (**1**) that fragments with a higher barrier (either enthalpic or free energy) than that of the unsubstituted system (**2**). Overall, the relative effect of substituents in governing the barriers associated with the fragmentation of 1,4,2-oxaselenazoles is in good qualitative agreement with recently reported experimental observations for the fragmentation of the closely related 1,4,2-oxathiazole (i.e., where Se is replaced with S) derivatives. [22]

The inclusion of solvent, in this case acetonitrile (which we have selected on the basis of its use in previous experimental studies pertaining to the fragmentations of closely related 1,4,2-oxathiazole systems), [22] results in notable increases in exergonicity, by amounts ranging from 0.2 kJ mol^{-1} in the case of system **7** to 23.4 kJ mol^{-1} in the case of system **15**. The greater reduction in free energy in the case of system **15** arises, in minor part, because the free energy of solvation correction for heterocycle **15** is 6.2 kJ mol^{-1} less exergonic than that for system **7**, but mainly because the carbonyl product formed from system **15** (namely $(Me_2N)_2CO$) has a significantly more exergonic free energy of solvation correction (–32.9 kJ mol^{-1}) than that of the carbonyl product formed upon fragmentation of system **7**, namely $(NC)_2CO$ (which has a free energy of solvation correction of –15.8 kJ mol^{-1}). The more favorable solvation correction for $(Me_2N)_2CO$ versus $(NC)_2CO$ is consistent with the fact that the former possesses a much greater gas-phase dipole moment than the latter (3.154 Debye versus 0.635 Debye, at the B3LYP/6–31G(2df,p) level of theory). Concerning the free energy barriers, inclusion of solvation corrections serves afford free energy barriers ($\Delta G^{o,\ddagger}_{(MeCN)}$) that are lower than those in the gas phase, with reductions ranging from 4.0 kJ mol^{-1} in the case of system **7** to 25.8 kJ mol^{-1} in the case of system **15**. The greater reduction in the case of system **15** vs **7** arises because of the fact that (i) the free energy of solvation correction for heterocycle **15** is 6.2 kJ mol^{-1} less exergonic than that for heterocycle **7**, and (ii) the transition state associated with fragmentation of **15** is significantly more stabilized than that arising upon fragmentation of **7** (with free energy of solvation corrections of –53.5 vs –37.9 kJ mol^{-1}, respectively). Finally, the relative effect of substituents in governing the free energy barriers in acetonitrile is, for the most part, unchanged compared with the relative ordering in the gas phase (in fact a plot of $\Delta G^{o,\ddagger}_{(gas)}$ vs $\Delta G^{o,\ddagger}_{(MeCN)}$ results in a linear relationship with $R^2 = 0.9906$). In this regard system **1** retains its position of having the highest $\Delta G^{o,\ddagger}_{(MeCN)}$ value (180.8 kJ mol^{-1}), whilst system **15** has the lowest ($\Delta G^{o,\ddagger}_{(MeCN)} = 42.0$ kJ mol^{-1}). The finding that solvation in a polar solvent such as acetonitrile reduces the free energy barriers associated with fragmentation is consistent with previous experimental reports concerning the fragmentation of 1,4,2-oxathiazole derivatives (in which Se is replaced with S), whereby performing reactions in polar solvents resulted in a decrease in the required temperature to induce fragmentation, whilst also affording higher yields of isothiocyanate product. [10]

4. Conclusions

In this study, the reactions of fifteen 1,4,2-oxaselenazole derivatives that fragment into the corresponding carbonyl derivatives and methyl isoselenocyanate have been studied using the high-level CBS-QB3 thermochemical protocol. The effect of substituents (both electron donating and electron withdrawing) at the C5-position has been surveyed, and for these systems a Bell-Evans-Polanyi relationship is observed. In the gas-phase, substitution at the C5-position with a single CF_3 substituent affords the heterocycle with the largest free energy barrier to fragmentation (190.1 kJ mol^{-1}), whilst substitution with two dimethylamino substituents affords the system with the lowest free energy barrier (67.8 kJ mol^{-1}). The introduction of solvent (in this case acetonitrile) serves to lower the free energy barriers (by amounts ranging from 4.0 to 25.8 kJ mol^{-1}), with the two aforementioned heterocycles having free energy barriers in acetonitrile of 180.8 and 42.0 kJ mol^{-1}, respectively. Overall, the results of this study broadly indicate that the presence of electron-donating substituents (particularly amino groups) at the C5-position afford heterocycles which offer the most efficient (in terms of fragmentation kinetics) routes to the preparation of isoselenocyanates.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cdc.2017.04.003.

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