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Slow homolytic substitution reactions at selenium: 2-Selenabicyclo[1.1.1]pentane

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ABSTRACT

Ab initio molecular orbital and density functional calculations predict that 3-(alkylseleno)cyclobutyl radicals (**12**) undergo intramolecular homolytic substitution chemistry to form 2-selenabicyclo[1.1.1]pentane (**14**) with energy barriers ($\Delta E_1^{\ddagger}$) that depend on both level of theory and nature of the leaving radical. In the absence of electron correlation, HF/6-311G(d,p) calculations provide values of $\Delta E_1^{\ddagger}$ that range from 170.6 (*t*-Bu) to 206.5 kJ mol^{-1} (Me). Inclusion of electron correlation (QCISD, CCSD(T)) serves to reduce these barriers by 30–40 kJ mol^{-1}. At the highest level (G3(MP2-RAD)), activation energies of 150.0 (Me), 143.3 (Et), 138.0 (*i*-Pr), 129.7 (*t*-Bu) and 108.4 (Bn) kJ mol^{-1} are calculated. G3(MP2)-RAD also provides rate constants for ring-closure (k_c) that range from 5×10^{-14} (Me) to 2×10^{-8} s^{-1}(Bn) suggesting that this chemistry is unlikely to be useful for constructing these interesting ring systems. Data for the cyclization for the analogous sulfur-containing system, the 3-(alkylthio)cyclobutyl radicals (**15**) are also provided.

1. Introduction

Selenium is the least abundant element on Earth with a defined role in human biology [1]. Despite toxic effects having been reported as early as 1295 [2], it is now well recognised that a healthy human diet requires around 55–70 μg of selenium per day [3]. The amino acid selenocysteine is the principal form by which mammals use selenium for biological advantage [4], and its presence across most living kingdoms has seen it regarded as the 21st essential amino acid [5].

While similarities between selenium and its smaller cousin, sulfur, are to be expected, the greater reactivity of selenium in enzymes such as glutathione peroxidases, thioredoxin reductase and iodothyronine deiodinase is necessary for proper biological function [6]. These differences are largely the consequence of the superior antioxidant capacity of organic selenides when compared to the analogous sulfur-containing compounds [7], increased nucleophilicity as well as faster reactions with organic free radicals [8], key features of selenium-containing molecules that we have exploited in synthesis [9].

For over two decades, we and others have prepared selenium-containing heterocyclic compounds through the use of free radical chemistry as well as other methodology [8,9]. Some of the compounds prepared are curiosities [10–14], while many have important biological properties. These include antioxidants and anti-inflammatory agents (eg. **1**, **2**) [7,15,16], antibiotic and β-lactamase inhibitor analogues (**3**) [17], cardioprotective agents (**4**) [18,19], antihypertensives (**5**, **6**) [20,21], and selenium-containing carbohydrates (**7**) that are potent water-soluble antioxidants that also accelerate skin tissue repair (wound healing) [22,23] (see Structures 1–7).

Despite having successfully employed intramolecular homolytic substitution chemistry for the preparation of many of these compounds, it was only recently that we began to question the assumed mechanism for the S_H2 process, since sulfones were reported as being incapable of reacting by radical substitution chemistry [24,25]. This observation, together with high-level computational studies highlighted the importance of the lone-pairs of electrons on the chalcogen atom, in turn requiring a reevaluation of the mechanism of the S_H2 process (Scheme 1) [24].

Concurrent with our synthetic endeavours, especially given the importance of rate data for radical reactions [26], we have also been determining kinetic parameters and developing a kinetic scale for homolytic substitution reactions at chalcogen. This work, which has involved a combination of computational and laboratory-based techniques, has yielded rate constants (k_c) for ring-closure that span approximately 45 orders of magnitude, from 2×10^{-37} (25°) for the ring closure at the sulfone sulfur in **8** [24], to

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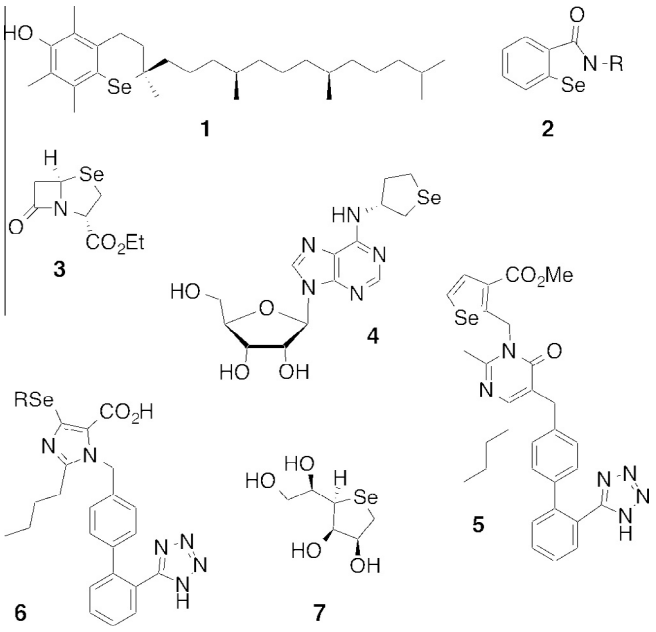
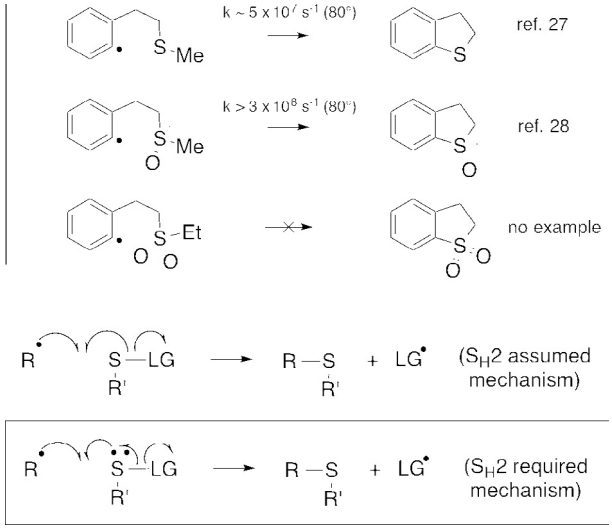


Structures 1–7.

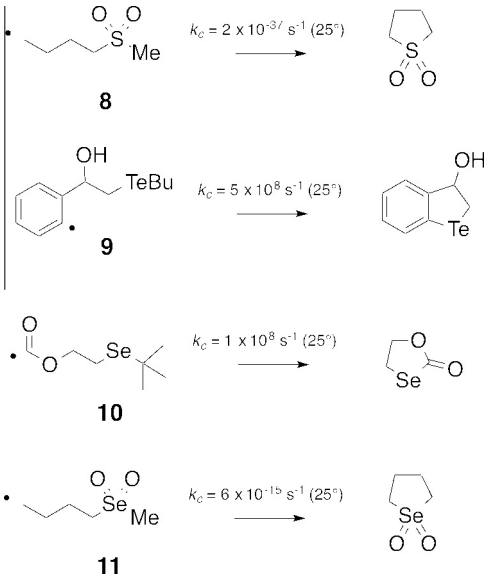


Scheme 1. (See above-mentioned references for further information.)

$5 \times 10^8\ s^{-1}$ (25°) for the cyclization at the tellurium atom in **9** [29]. Values of k_c for radical ring closure at selenium have been found to span some 23 orders of magnitude, with the oxyacyl radical cyclizing at the selenide in **10** with a rate constant of $1 \times 10^8\ s^{-1}$ (25°) [30], while the selenone **11** ring closes with $k_c = 6 \times 10^{-15}\ s^{-1}$ at the same temperature (Scheme 2) [31].

Natural bond order (NBO) analyses of the transition states in these substitution reactions reveal that, contrary to expectation, and in difference to the S_N2 reaction, the dominant orbital interactions operating during the bond-forming and bond-breaking processes involve the unpaired electron and one, or both of the lone-pairs of electrons on the chalcogen atom [24]. As carbon-centered radicals are clearly electrophilic in this chemistry [24], the absence of at least one lone-pair of electrons on the atom undergoing substitution clearly renders this chemistry unviable.

Given the range in the collective rate data for intramolecular homolytic substitution chemistry at chalcogen, together with our interest in preparative chemistry involving selenium, we wondered whether or not it were possible to engineer a radical that would ring-close at a selenide (selenium atom containing its lone-pairs), but with a rate constant approaching that of a selenone (selenium atom devoid of its lone pairs). Clearly, this question is one of scientific curiosity, however, an answer to this question would allow us to more fully understand the homolytic substitution process and provide a more complete kinetic scale for this chemistry.



Scheme 2.

In this paper we report our recent computational work directed toward answering this question and report that the cyclization of the 3-(methylseleno)cyclobutyl radical (**12**, R = Me) to give 2-selenabicyclo[1.1.1]pentane is predicted to proceed with $k_c = 4.8 \times 10^{-14}\ s^{-1}$ (25°) using G3(MP2-RAD.

2. Computational methods

Ab initio and DFT calculations were carried out using Gaussian 09 [32]. Geometry optimizations were performed utilizing standard gradient techniques at HF, MP2 and BHandHLYP levels of theory using restricted (RHF,RMP2 and RBHandHLYP) and unrestricted (UHF, UMP2 and UBHandHLYP) methods for closed and open shell systems, respectively [33]. Standard basis sets were employed in all calculations. To obtain improved energies, single point ROMP2, QCISD and CCSD(T) calculations were performed on select BHandHLYP and MP2 optimized structures. B3LYP/6-31G(d) optimizations were performed on starting materials and transition states only as part of the G3(MP2)-RAD composite method (*vide infra*). Apart from some HF calculated structures, values of $\langle s^2 \rangle$ never exceeded 0.81 before annihilation of the first spin contaminant. After annihilation of quartet contamination $\langle s^2 \rangle$ ranged from 0.75 to 0.77. Zero point energy corrections have been applied to all optimized structures and all ground and transition state structures have been verified by vibrational frequency analysis. Optimized geometries and energies for all transition structures in this study are available in the Electronic Supplementary Material. Kinetic parameters were determined using the Eyring equation and energies obtained using the G3(MP2)-RAD method. G3(MP2)-RAD is a high-level composite method that has been shown to perform within chemical accuracy for radical reaction, hence it was selected for our study [34].