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A partial exploration of the potential energy surfaces of SCN and HSCN: Implications for the enzyme-mediated detoxification of cyanide

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ABSTRACT

Cyanide (CN) is considered to be a terrorist chemical weapon due to its ready availability in multi-kilogram quantities and multi-modal means of intoxication. The body uses the sulfur transferase enzyme rhodanese to detoxify cyanide via conversion of cyanide to thiocyanate. This paper explores the potential energy surfaces for the conversion of cyanide anion and hydrogen cyanide to thiocyanate anion and thiocyanic acid, respectively.

The potential energy surface for the conversion of cyanide anion to thiocyanate shows that the formation of thiocyanate (SCN) is vastly preferred to formation of its isomer SNC. However, the potential energy surface for the conversion of hydrogen cyanide to thiocyanic acid reveals that the formation of HSCN and HNCS would be relatively equal. The failure for analytical methods to detect HNCS is rationalized by the observation that deprotonation of either HNCS or HSCN leads to the same thiocyanate anion.

1. Introduction

Cyanide (CN) is considered to be a military or terrorist chemical weapon [1]. Its ready availability in multi-kilogram quantities, multi-modal means of intoxication (ingested as a solution in water or inhaled as an aerosol of hydrogen cyanide gas) makes it a deadly weapon in the terrorist's arsenal.

In the body, the detoxification mechanism for cyanide is believed to involve the enzyme rhodanese [2], although mercaptopyruvate transferase [3], albumin [4] and thioredoxin [5] can also act as sulfur transfer agents. Rhodanese, an enzyme found predominantly in the mitochondria [6], mediates the conversion of CN to the substantially less toxic thiocyanate (SCN). Excretion removes the detoxification product from the body. A schematic for the mechanism of rhodanese-mediated detoxification of cyanide [7] is shown in Fig. 1.

As represented in Fig. 1, several mechanistic questions arise; does cyanide anion or hydrocyanic acid (HCN) bind to the enzyme; how does sulfur add to the bound cyanide; is the formation of an alkyl thiocyanate synchronous (one-step), or does it require several steps? The key to answering these questions is investigation of the SCN and HSCN potential energy surfaces.

Examination of the potential energy surface of thiocyanate should begin to address a number of the questions raised above. This will determine the relative stability of SNC as compared to SCN. Mapping the potential energy surface should also indicate whether SNC and SCN interconvert, and if so, how. This study will provide insights into why only SCN is observed. In addition, the question of whether cyanide or HCN binds to the enzyme can be addressed. Further, this study should determine whether the chalcogenation of cyanide is a one- or multi-step process.

2. Methods

Quantum mechanics calculations were carried out using the Gaussian G03 revision C02 [8] package. All optimizations were carried out with Cartesian polarization functions. The identity of each minimum and transition states structure was confirmed by a frequency calculation. Natural Bond Order [9] calculations were carried out using the Gaussian package. The Gaussian-produced wavefunction files were generated with Cartesian d functions and analyzed with the AIM2000 [10] software package.

3. Results and discussion

The potential energy surface for SCN was originally calculated at two different levels of theory: MPW1PW91/6-311++g(2d,p) [11] and QCISD/6-311++g(2d,p) [12]. The combination of the MPW1PW91 DFT functional and Pople basis set has been shown

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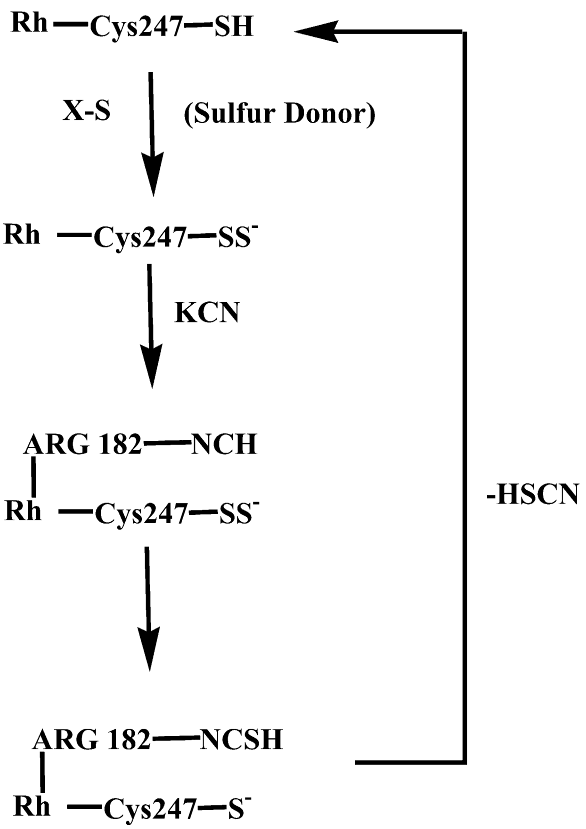

Fig. 1. This is a schematic representation of the chalcogenative detoxification of cyanide vis-à-vis rhodanese. Cysteine residue 247 reacts with a sulfur donor (*X*–S) to form the persulfide cysteine, activating the enzyme. Cyanide then binds to the enzyme. It is assumed that ARG-183 will hydrogen bond strongly to HCN, allowing a perpendicular orientation relative to the CYS-247 residue. The sulfur is then transferred to cyanide, forming thiocyanate. Thiocyanate is released from the enzyme, completing the catalytic cycle.

Table 1
Comparison of computed structural features for minima and transition states on the SCN potential energy surface. All distances given in units of Angstroms while all angles are in units of degrees.

Compound	MPW1PW91	QCISD	QCISD(T)
SCN			
r(S–C)	1.661	1.679	1.686
r(C–N)	1.170	1.161	1.173
<S–C–N	180.0	180.0	180.0
SNC			
r(S–N)	1.669	1.696	1.702
r(N–C)	1.171	1.161	1.183
<S–C–N	180.0	180.0	180.0
INT			
r(S–C)	2.006	2.140	2.084
r(S–N)	1.944	1.956	1.998
r(C–N)	1.215	1.199	1.224
<S–C–N	69.32	64.75	76.42
TS1			
r(S–C)	1.866	1.922	1.978
r(S–N)	2.385	2.385	2.231
r(C–N)	1.195	1.193	1.210
<S–N–C	100.0	92.27	62.06
TS2			
r(S–C)	1.913	1.979	1.983
r(S–N)	2.225	2.253	2.238
r(C–N)	1.193	1.183	1.209
<S–C–N	88.35	87.08	85.40

Table 2
Zero-point corrected energy differences for intermediates on the S–C–N potential energy surface. Both methods used the 6-311++g(2d,p) basis set.

Transition	MPW1PW91	QCISD	QCISD(T)
SNC → TS1	26.6	26.5	27.6
INT → TS1	2.68	0.38	1.19
INT → TS2	2.00	1.40	1.29
SCN → TS2	65.3	63.0	63.7
SNC → SCN	−36.02	−35.5	−36.0

to be exceptional at reproducing the experimental structures of first-row hydrides [13]; the results are often superlative to higher levels of theory. The inclusion of a variational configuration interaction method (QCISD) was done to more accurately determine the structure and energy for transition state structures. While there are DFT methods parameterized for kinetic data [14], the improved energetics comes at the expense of less accurate ground state structures. The variational MPW1PW91 method allows for a reasonable computation of transition barrier heights, the results of which can be refined at the QCISD level of theory. The structures obtained from these methods are summarized in Table 1, while energy differences between structures on the potential energy surface are summarized in Table 2.

From the data in Table 2, it is clear that SCN is energetically favored over SNC by 36.0 kcal/mol after correcting for zero-point energies. This is in reasonable agreement with the energy difference computed with the QCISD method. This substantial energy difference can account for the lack of SNC observed *in vitro*.

The exploration of the SNC to SCN potential energy surface began with the assumption that a single transition state connected the two structures. Initial attempts to locate a single, unique SNC to SCN transition state were unsuccessful. Depending on the initial structure of the putative single transition state, two different structures were found: TS1 and TS2. TS1 was found by searching for a transition state with SNC as a starting point; TS2 was found when using SCN as a starting point. Therefore, another structure had to lie between these two transition states.

Several attempts were made to locate this structure. No second order saddle points could be found. However, perturbation of either the TS1 or TS2 structure followed by geometry optimization, lead to the identification of the same third minimum on the potential energy surface. This minimum (INT) lies between the structures TS1 and TS2 on the SCN potential energy surface. The energy for each structure is shown in Table 1 while the structures for each structure are summarized in Table 2. A representation of the computed potential energy surface is shown in Fig. 2.

The electron density topology quantities atomic monopole (charge), atomic dipole, atomic volume and electron density at the bond critical point for SCN and SNC are summarized in Table 3. The first observation made was that the electron density at the bond

Table 3
Atomic monopole and atomic dipole values (q and m, respectively) for the atoms in SCN and SNC. The electron density at the bond critical point (r) for the bonds in both SCN and SNC. All values were derived from wavefunctions computed at the MPW1PW91/6-311++g(2d,p) level of theory.

Molecule	q (S)	q (N)	q (C)	μ (S)	μ (N)	μ (C)	ρ (S–N)	ρ (S–C)	ρ (C–N)
SCN	−0.262	−1.315	0.579	1.102	0.243	1.244		0.207	0.469
SNC	−0.112	−1.504	0.614	1.398	0.551	1.874	0.185		0.439