

Studies on Sulfenamides. XV. Semi-Empirical Calculation of Reactivity of 4'-Substituted Benzenesulfenamidyl Radicals

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The mechanism of the formation of 2,7-disubstituted phenazine in the oxidation of 4'-substituted benzenesulfenamides was studied by employing the PM3 method. Calculation of the total energy suggested that the homolytic cleavage of the S–N bond of cation radical (A) derived from benzenesulfenamides was not a spontaneous reaction at room temperature. The following mechanism has been suggested. Dimerization of A followed by proton migration gives (4-substituted phenyl) (5-substituted-2-(phenylthioamino)phenylthioamine) (5), which is oxidized to give a cation, which is then cyclized to give 2,7-disubstituted 5,10-phenylthio-5,10-dihydrophenazine (6). The acid hydrolysis of 6 gives diphenylthiosulfinate and 2,7-disubstituted-5,10-dihydrophenazine, and the latter is oxidized to 2,7-disubstituted phenazine by dissolved oxygen in the reaction solution.

Key words PM3; sulfenamide; phenazine; radical; radical cation; oxidative dimerization

The oxidation of 4'-substituted benzenesulfenamides (OMe (**1a**), Me (**1b**), Cl (**1c**)) has attracted chemists' attention because it has easily produced benzenesulfenamidyl radicals (4'-OMe (Aa), 4'-Me (Ab), 4'-Cl (Ac)) and yielded phenazines as one of final products.^{1–12} The coupling of benzenesulfenamidyl radicals also seems interesting from a synthetic viewpoint for one-pot synthesis of 2,7-disubstituted phenazines (OMe (**2a**), Me (**2b**), Cl (**2c**)).¹² However, the mechanism of the formation of the phenazine ring has been unclear. Sayo *et al.* and Benati *et al.* proposed the mechanism of the formation of **2** independently, but their two mechanisms are apparently incompatible with each other.

Sayo carried out the oxidation of **1** using lead dioxide and an electrochemical method, and obtained **2** and diphenyl disulfide (**3**) as the products.^{1–5} The presence of A in the reaction solution was proved by using electron spin resonance (ESR) and visible spectra.³ The reaction products have been explained on the basis of the homolytic cleavage of the S–N bond of A, which afforded a phenylthio radical (B) and nitrenium; the former dimerized to **3** and the latter dimerized to **2**, as shown in Chart 1.

On the other hand, Benati reported that the oxidation of **1a** with lead dioxide at 30 °C had afforded *N,N*-bis(phenylthio)-*p*-anisidine, **2a** and **3** where as at 10 °C *N,N*-bis(phenylthio)-*p*-anisidine and di-imines which might be 1-[aza(2-azaphenylthiomethylene)-5-methoxycyclohexa-3,5-dienylidene]methyl]-4-methoxybenzene were observed.¹¹ The later was thermally unstable and thus gave **2a** and **3**. Benati concluded that the dimerization of A could explain the formation of the products, as shown in Chart 2.

Then, molecular orbital (MO) calculation was applied to elucidate the reactivity of A, as well as the mechanism of the formation of **2**. Although the oxidation of **1** gives various products, this paper was confined to studying the mechanism of phenazine formation to avoid a confused discussion.^{6,10,13}

Results and Discussion

At first, the possibility of homolytic cleavage of the S–N bond of A was examined. Total energies of A, the phenylthio radical and nitrenes were calculated and are summarized in Table 1.

The geometry search was carried out by MM⁺, then parametric method 3 (PM3) was used to optimize the structure.

The elementary process of homolytic cleavage of the S–N bond of A requires 66–98 kcal/mol reaction heat (ΔH). Therefore, the homolytic cleavage of the S–N bond of A does not seem to be a spontaneous reaction at room temperature.

In order to examine the possibility of the dimerization of A, the total energy of [2-(azaphenylthiomethylene) cyclohexa-3,5-dienyl]phenylphenylthioamines (**4**) was calculated

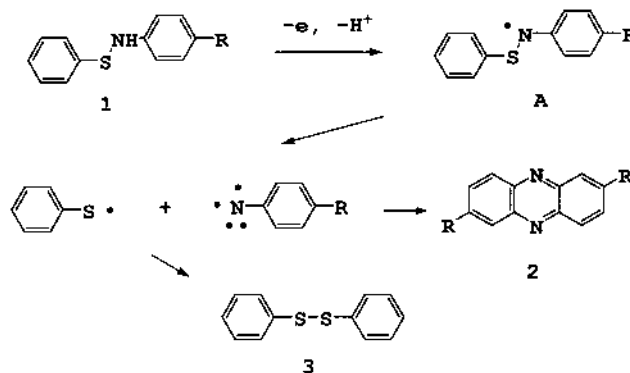


Chart 1

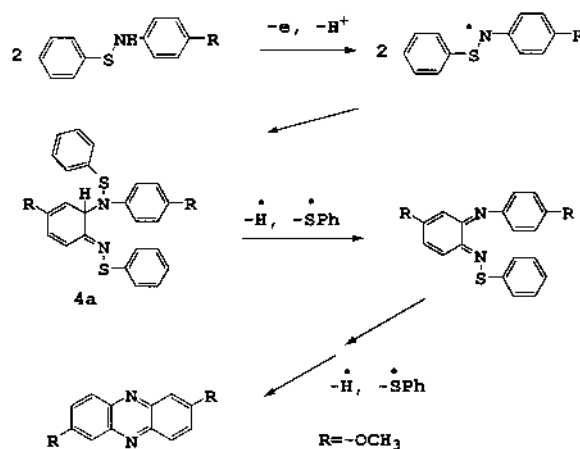


Chart 2

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Table 1. Total Energy of Radical and Nitrene

Intermediate	Total energy (kcal/mol)
Aa	-54555.47
Phenylthio radical	-22424.19
4-Methoxyphenyl nitrene ^{a)}	-32034.57 (-54458.76 ^{b)})
4-Methoxyphenyl nitrene ^{c)}	-32065.44 (-54489.63 ^{b)})
Ab	-47794.61
4-Methyphenyl nitrene ^{a)}	-25272.76 (-47696.95 ^{b)})
4-Methyphenyl nitrene ^{c)}	-25304.39 (-47728.58 ^{b)})
Ac	-51292.83
4-Chlorophenyl nitrene ^{a)}	-28769.97 (-51194.16 ^{b)})
4-Chlorophenyl nitrene ^{c)}	-28802.27 (-51226.46 ^{b)})

a) Singlet state. b) The sum of the total energies of phenylthioradical and that of nitrenes. c) Triplet state.

Table 2. Total Energy of Dimer of A

Compd.	Total energy ^{a)} (kcal/mol)
4a	-109111.62 (-1091109.40)
4b	-95591.70 (-95589.22)
4c	-102583.06 (-102585.66)
5a	-109133.14 (-1091109.40)
5b	-95612.20 (-95589.22)
5c	-102607.88 (-102585.66)

a) Double of total energy of corresponding A is shown in parentheses.

and the results are shown in Table 2. The total energies of **4a** and **4b** are lower than double that of corresponding A, but that of **4c** is higher than that of Ac by 2.6 kcal/mol. Then, a proton migration reaction of **4** was assumed and total energies of (4-substituted phenyl) [5-substituted-2-(phenylthioamino)phenyl]phenylthioamine (**5**), which were the products of the proton migration, were calculated. The results were also shown in Table 2. The total energies of **5a—c** are lower than double that of corresponding A, by 21–25 kcal/mol.

These results show that the homolytic cleavage of the S–N bond of A is difficult, and the dimerization of A proceeds spontaneously at room temperature as Benati predicted.⁶⁾ These results may also explain the solvent effect of the formation of 2,7-dichlorophenazine.^{2,11)} Using acetonitrile as a solvent, the oxidation of **1c** gave a 13–64% yield of 2,7-dichlorophenazine. Switching the solvent to benzene, the yield of 2,7-dichlorophenazine was deduced to 0–1%.^{3,11)} An aprotic solvent, benzene, may inhibit the proton migration of **4c**.

Other dimers of Ac were also examined and the results are shown in Table 3.

The results suggested that **5c** was the most stable of all.

Before the cyclization, compound **5** must be oxidized and lose a proton, just like **1**, to give radical (B). The possible fates of the radical derived from **5c** are summarized in Chart 3, and total energies are also shown.

If B cyclizes directly to give radical C, whose total energy is -102222.96 kcal/mol, then ΔH is a slightly positive value (0.2 kcal/mol).

When the homolytic cleavage of the S–N bond of B is assumed, the products are nitrene F and a phenylthio radical, and their total energy is -79938.33 kcal/mol and -22424.19 kcal, respectively. Therefore, ΔH is 60.64 kcal/

Table 3. Total Energy of Dimer of Ac

Structure	Total energy (kcal/mol)
	-102579.98
	-1025693.05
	-102571.71
	-102584.57

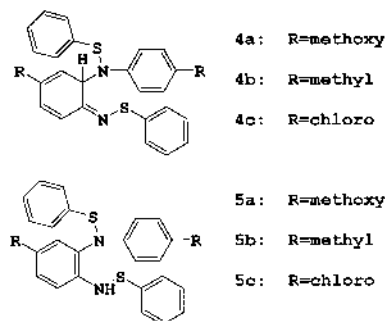


Chart 3

mol, and this reaction will not proceed spontaneously at room temperature.

When the oxidation of radical B is assumed, the product is a nitrenium ion D and which cyclize to E. The total energies of D and E are -102059.87 kcal/mol and -102071.69 kcal/mol, respectively, so ΔH is a negative value that is -17.43 kcal/mol. Therefore the most reasonable fate of B is the oxidation which produces D. Deprotonation of E gives 2,7-dichloro-5,10-phenylthio-5,10-dihydrophenazine (**6**).

The homolytic cleavage of two S–N bonds of **6** may give 2,7-dichlorophenazine and two phenylthio radicals, the latter dimerizing to diphenyldisulfide. However, ΔH of the homolytic cleavage of the S–N bond of **6** is 68.99 kcal/mol, so this reaction is ruled out.

Next, acid hydrolysis was proposed to cleave the S–N bond of **6**. As the oxidation of **1a—c** proceeds, the reaction solution begins to be acidic, and acid hydrolysis of the S–N bond is a well known reaction.^{14,15)} The acid hydrolysis of **6** gives 2,7-dichloro-9,10-dihydrophenazine and diphenylthio-sulfate. The oxidation of the former by the dissolved oxygen in the reaction solution gives **2C**. Disproportionation of the latter gives **3** and diphenylthiosulfonate.¹⁶⁾

A detailed study concerning another product is in progress.

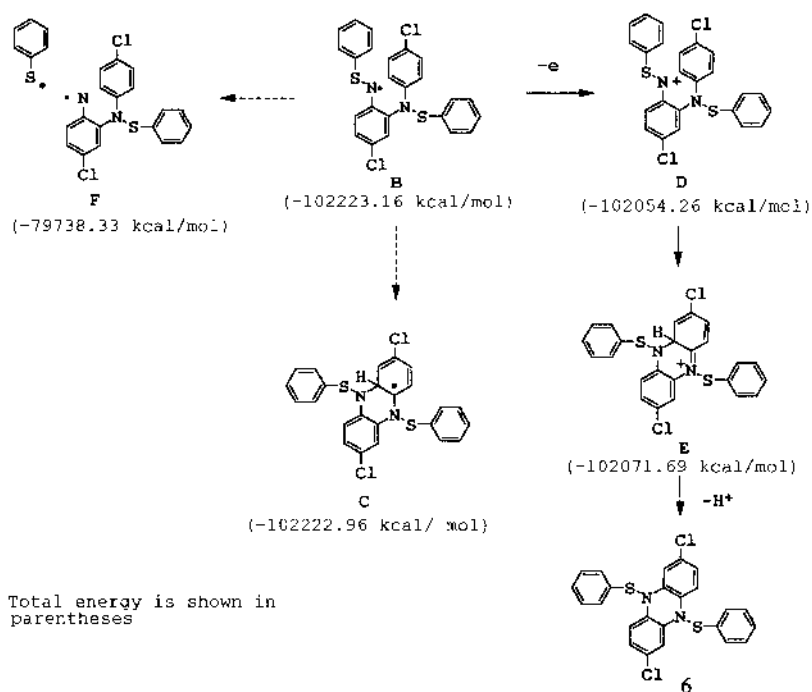


Chart 4

Experimental

Apparatus MO calculation was carried out using Dell Dimension XPS R400 personal computers running HyperChem release 5.1 (Hypercube, Inc., Canada).

Semi-Empirical Calculation PM3 was used. Before single point calculation, geometry optimization was carried out with MM⁺ at first, then with UHF (spin unrestricted Hartree-Fock) calculation using Polak-Ribiere as the minimization algorithm until the total root-mean-square (RMS) gradient was reduced to 0.01 kcal/(Å mol).

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