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Studies in sulfur-nitrogen nucleophilicity

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Abstract

As part of a study of nitrogen vs sulfur nucleophiles, the behavior of methylation products from dimethyl-(2-methylthioethyl)amine $CH_3SCH_2CH_2N(CH_3)_2$ **1** is described. Of the 2 potential products (a sulfonium salt or an ammonium salt), the ammonium salt from *N*-methylation **2** dominated. The isomeric sulfonium salt **3** prepared by an independent route was found to be unstable and rearranged to the isomeric ammonium salt. The rearrangement pathway was investigated using deuterium-labeled reactants. The sulfonium salt **3** also produced a piperazinium double salt **9** on heating. The reaction pathway was also followed by deuterium labeling. The results support the conclusion that production of the double salt **9** involves intermediate formation of *N*,*N*-dimethylaziridium ion **4**.

KEYWORDS

Nucleophilicity, rearrangement, sulfonium salt

1 | INTRODUCTION

This paper is a modest contribution to the field of physical organic chemistry, but it comes with deep appreciation and recognition of the profoundly important contributions made by John D. Roberts to the field throughout his long career. It is a privilege to offer this paper for inclusion in the special issue of the journal in recognition of Robert's lifetime scientific achievements and the impact he has had on generations of students and colleagues.

The work described here is a continuation of a study reported some years ago,[1] but the science remains relevant and, we hope, of continuing interest. It concerns the comparative strengths of sulfur and nitrogen nucleophiles. Multiple factors contribute to nucleophilicity arising from the donation of a lone electron pair on the donor atom to an acceptor electrophile. In qualitative terms, they include size and structure of the nucleophile, its electronegativity, polarizability, oxidation potential, basicity, and external influences such as solvent, molecular environment, and, importantly, sensitivity to the approaching electrophile. These factors are embodied in the prevailing theory of hard vs soft acids and bases, nucleophiles, and electrophiles,[2] and the related theory of control by interacting frontier molecular orbitals.[3]

Our initial interest was in structural effects of bifunctional molecules such as when molecules with both sulfide and amine functions compete for a common electrophile. The molecular framework chosen for study was a $RS(CH_2)_nNR_2$ system with n = 0, 1, or 2, the objective being to determine how the proximity of sulfide and amine functions affect their nucleophilic behavior to different electrophiles.

The results of our earlier study[1] confirmed that, regardless of the S/N proximity, nitrogen is the preferred site of protonation *and* methylation. This is consistent with much related evidence that tricoordinate nitrogen is more basic than dicoordinate sulfur and more nucleophilic than sulfur to hard electophiles (eg, CH_3^+). However, sulfur rather than nitrogen is the preferred site of attack by soft electrophiles (eg, CH_3S^+)—consistent with the general observation that soft nucleophiles prefer soft electrophiles and hard nucleophiles prefer hard electrophiles.[2,3]

$R_2N(CH_2)_nSR$
n = 0, 1, 2

H^+ attack at N
R^+ attack at N
RS^+ attack at S

Whereas proximity of the sulfur and nitrogen atoms does not appear to invert their relative basicity, or nucleophilicity, it does influence the product distribution. For n = 0 and n = 1, reactions with electrophiles resulted in complex products of S—C and N—C cleavage.[1] However, with n = 2, the initial products formed with the same electrophiles did not result in immediate cleavage of the S or N heteroatoms, implying that the hetero atoms are sufficiently distant for their interaction to be minimal. However, several features of the chemistry observed for the n = 2 system proved to be interesting and worthy of further investigation. This is the focus of the current study described here.

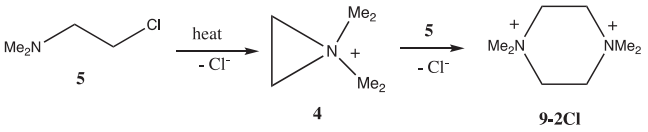
2 | REARRANGEMENT REACTIONS AND ALKYL TRANSFER FROM SULFUR TO NITROGEN

In earlier work,[1] we found that methylation of dimethyl-(2-methylthioethyl)amine **1** with 1 equivalent of Me_3O^+ BF_4^- gave the ammonium salt **2-BF4**. There was no evidence of S-methylation of **1** to produce the isomeric sulfonium salt **3-BF4** although **1** reacted with 2 equivalents of Me_3O^+ BF_4^- to give the ammonium sulfonium double salt **6-2BF4**. The isomeric sulfonium salt **3-BF4** was successfully prepared by an independent route involving protection of the amine function of **1** by N-protonation followed by S-methylation to the sulfonium-ammonium double salt **6-HBF4.BF4** and deprotonation to the sulfonium salt **3-BF4** (Scheme 1). However, it was not possible to obtain a pure sample of **3-BF4** because it slowly rearranged at ambient temperature to the isomeric ammonium salt **2** by methyl transfer from sulfur to nitrogen. After 10 days, the ratio of **2** to **3** reached 3:2, but we cannot be sure this represents the equilibrium composition as we have no evidence of the reverse rearrangement of **2** to **3** (Scheme 1). Experimental details are provided as Supporting Information accompanying this article.

3 | DIMERIZATION AND ELIMINATION

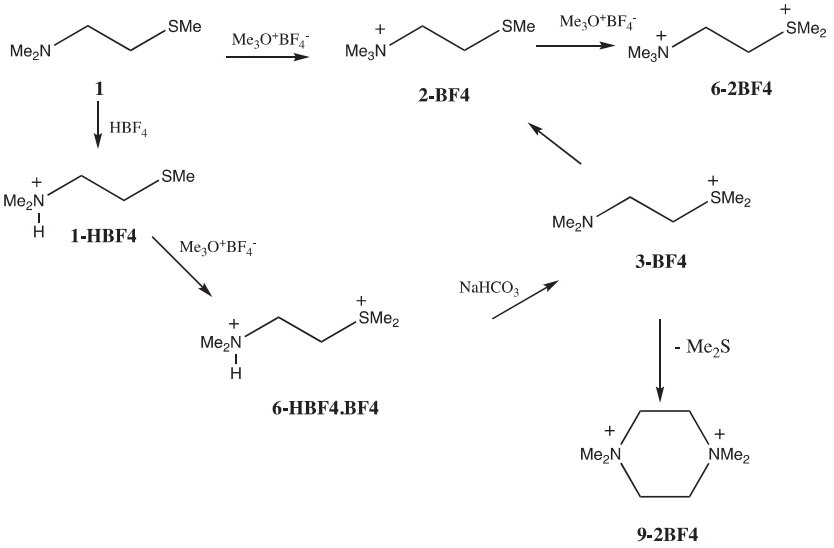
On heating, a second notable reaction of **3-BF4** occurred. At 100°C in nitromethane or acetonitrile, **3-BF4** rapidly eliminated dimethylsufide and formed a high-melting white crystalline solid identified as *N*,*N*,*N*,*N*-tetramethy lpiperazinium fluoroborate **9-2BF4** (Scheme 1).

The formation of **9** as the chloride double salt was previously reported by Bartlett et al from the structurally related dimethyl-(2-chloroethyl)amine **5**.[4] Kinetic studies led these workers to conclude that the transformation involves the intermediacy of an aziridium ion **4** which undergoes further reaction with **5** to form the corresponding piperazinium double salt **9-2Cl** (Equation 1).



(1)

Synthesis and isolation of stable aziridium salts have been reported,[5] and mechanistic studies of piperazine formation from aziridines have also appeared in the literature.[6] Thus, it seems entirely plausible that aziridium intermediates may also be involved in the transformation of **3-BF4** to **9-2BF4**. The only difference between the Bartlett system and ours is the leaving group (Me_2S vs Cl^-). We therefore decided to investigate the formation of **9** by deuterium labeling in the parent **3** to probe for the evidence of an aziridium intermediate. We also used labeled **3** to investigate its rearrangement to **2**.



SCHEME 1 Methylation Reactions of Dimethyl-(2-methylthioethyl)amine **1**

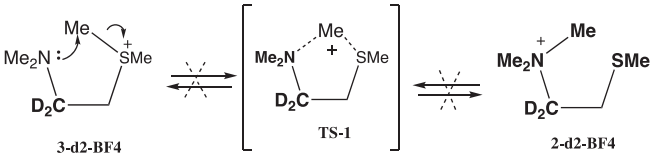
4 | SYNTHESIS OF DEUTERIUM-LABELED SULFONIUM SALT 3-d-2BF4 FROM DIMETHYL-(2-METHYLTHIOETHYL) AMINE 1-d2

Deuterium labeled **1-d2** was prepared by the sequence shown in Scheme 2. Dimethylamine with chloroacetyl chloride gave the corresponding chloroacetamide. Displacement of chloride with methanethiolate followed by reduction with lithium aluminum deuteride (LAD) gave **1-d2**. It was necessary to protect the amine nitrogen of **1-d2** by protonation with HBF4 to methylate **1-d2** at sulfur to produce the sulfonium salt **3-d2-BF4**.

5 | REARRANGEMENT OF 3-d2

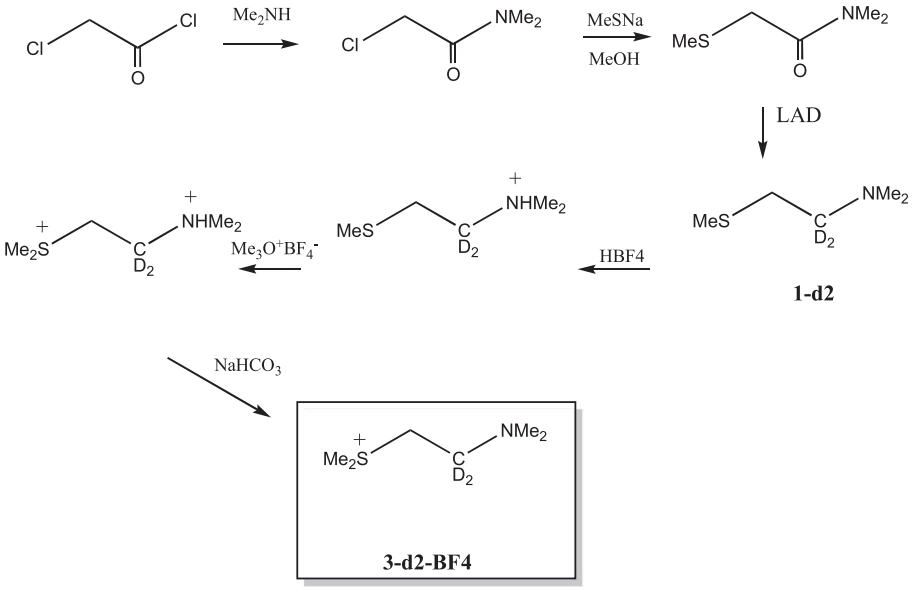
The methyl migration process of salt **3-d2** was followed by 1H and 13C NMR using an equimolar mixture of **3-d2** as the BF4 salt with triethylamine in nitromethane. The purpose of adding triethylamine was to determine whether, under the conditions of rearrangement, **3** also transfers an S-methyl group to the triethylamine nitrogen. If so, this would be evidence for an intermolecular methyl transfer process. During 4 weeks at room temperature in a sealed tube, the 1H signal intensities of **3-d2-BF4** (ppm; 2.29 ($\mathbf{CH_3)_2}$N, 3.52 ($\mathbf{CH_2}^+$S), and 2.91 ($\mathbf{CH_3)_2}$S$^+$) slowly diminished as the intensities of those of the isomeric ammonium salt **2-2d-BF4** (ppm: 2.18 ($\mathbf{CH_3}$S), 2.96 ($\mathbf{CH_2}$S), and 3.22 ($\mathbf{CH_3)_3}$N$^+$) increased proportionally. There was *no* evidence of methyl(triethyl)ammonium salt formation. Also, there was no 1H NMR evidence of products that might be expected from intermolecular methyl transfer from **3-d2-BF4** to another **3-d2-BF4** to give **1-d2** and a double salt **6-d2-2BF4** (Table 1). And, importantly, after most of the **3-d2** had rearranged to the isomeric ammonium salt **2**, there was *no* evidence of rearrangement of the deuterium-labeled methylene in either the remaining reactant **3-d2** or in the product **2-d2**.

The absence of crossover products and label shuffling support our initial, seemingly obvious, conclusion that rearrangement of **3** to **2** is intramolecular by way of a 5-membered transition state **TS-1**, as represented in Equation 2.



(2)

However, we were reminded by perceptive reviewers that the SN2 transition state depicted in Equation 2 is a 5-endo-tet cyclic process that is highly unlikely for geometric reasons. An SN2 transition state requires a large bond angle between the nucleophile, the electrophile, and the leaving group. That geometry is necessary for the HOMO-LUMO interacting orbitals to achieve bonding through a 180° backside approach of the nucleophile, which is not possible within the 5-membered endocyclic molecular structure of **TS-1**.[3,7] We have to conclude that the evidence in support of an intramolecular rearrangement is inconclusive. To distinguish between intramolecular vs intermolecular rearrangement would require application of the *endocyclic restriction test*.[8] This test



SCHEME 2 Preparation and Methylation of Deuterium-labeled Dimethyl-(2-methylthioethyl)amine **1-d2**

TABLE 1 Proton chemical shifts (ppm) of ammonium and sulfonium salts

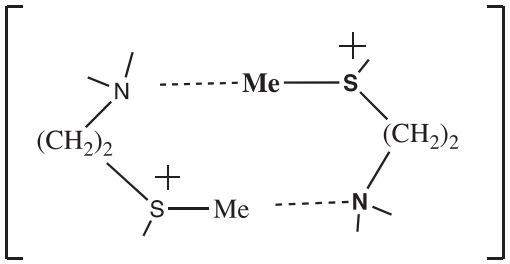
Structure	MeN+	MeN	MeS+	MeS	CH_2S+	CH_2S	CH_2CO	CH_2N
$ClCH_2CON(me)_2$		2.99(s)					4.07(s)	
$MeSCH_2CON(me)_2$		2.94(s)		2.06(s)			3.15(s)	
		2.83(s)						
$MeSCH_2CD_2N(me)_2$		2-25(s)		2.12(s)		2.59(s)		
(1-d2)								
$MeSCH_2CD_2N(me)_2HCl$	2.80(d)			2.18(s)		2.95		
(1-D2-HCl)								
$Me_2SCH_2CD_2N(me)_2H\ 2BF_4$	3.16(d)		3.12(s)		3.82(S)			
(6-d2-HBF4.BF4)								
$Me_2SCH_2CD_2N(me)_2\ BF_4$		2.29(s)	2.91(s)		3.52(s)			
(3-d2-BF4)								
$MeSCH_2CD_2N(me)3\ BF_4$	3.22(s)			2.18(s)		2.96(s)		
(2-d2-BF4)								
8a-d4		2.29(s)						2.45(s)
8b-d4		2.29(s)						2.45(s)
9-d4-2BF4[a]	3.51(s)				4.04 (CH2N+)			

Spectra were recorded at 300 MHz in $CDCl_3$ for neutral compounds and in CD_3NO_2 solution for salts.

[a]Produced from **3-d2-BF4** as a mixture of **9a-d4-2BF4** and **9b-d4-2BF4**.

has been used in related 5, 6, and 7-endo cyclizations and shown to support an intermolecular process.

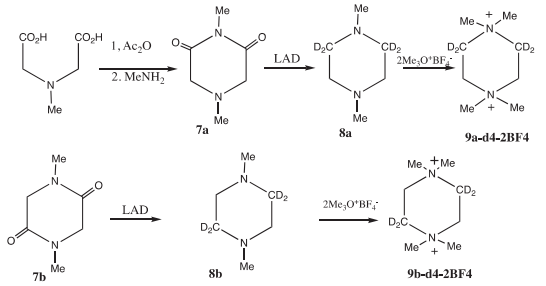
Larger ring endocyclizations could accommodate the large bond angle required for a typical SN2 displacement.[8b] A conceivable pathway for the conversion of **3** to **2** as a double SN2 intermolecular rearrangement by way of the transition state shown diagrammatically as **TS-2** would be consistent with the experimental data thus far. Synchronous methyl transfers would amount to an allowed 10-endo-tet configuration for **TS-2**. However, *double labeling* experiments are required for an endocyclic restriction test to definitively test for crossover products anticipated from **TS-2**. Rearrangement by way of a methyl radical (a single electron transfer (SET) mechanism) is also conceivable, but, as far as we know, no positive evidence for SET cyclization has been reported.[8b] But, in the absence of further experiments, the mechanistic details remain unresolved.



TS-2

6 | DIMERIZATION OF 3-d2 WITH ELIMINATION OF Me_2S

The labeled fluoroborate sulfonium salt **3-d2-BF4** was subjected to the same reaction conditions known to lead to dimethylsufide elimination and dimerization of unlabeled **3** to give the piperazinium double salt **9-2BF4**. Determination of the label distribution in the labeled product **9-d4-2BF4** by NMR was not possible, partly because of low solubility but primarily because the spectra of **9a** and **9b** are indistinguishable. The 1H NMR of a mixture of **9a** and **9b** produced on heating **3-d2-BF4** showed only 2 resonances corresponding to the $(Me)_3N^+$ resonance at 3.51 ppm and the CH_2N^+ resonance at 4.05 ppm. Instead, we chose to use IR spectroscopy to analyze for the label distribution. This proved to be



SCHEME 3 Preparation of Deuterium-labeled Piperazinium Salts **9-d4-2BF4**

TABLE 2 Carbon-13 chemical shifts (ppm) of ammonium and sulfonium salts

Structure	MeN+	MeN	MeS+	MeS	CH_2S+	CH_2S	CH_2CO	CH_2N
$ClCH_2CON(me)_2$		38.25		16.11		35.65	169.34	
$MeSCH_2CD_2N(me)_2$		45.97		16.40		32.5		
(1-d2)								
$MeSCH_2CD_2N(me)_2HX$	43.18			15.60		28.44		
(1-d2-HCl)								
$Me_2SCH_2CD_2N(me)_2H$ 2X	45.49		26.59		38.65			
(6-d2-HBF4.BF4)								
$Me_2SCH_2CD_2N(me)_2$ X		45.20	25.8		44.35			
(3-d2-BF4)								
$MeSCH_2CD_2N(me)_3$ X	53.23			14.38		25.88		
(2-d2-BF4)								
8a-d4		54.95						45.95
8b-d4		54.87						45.98

Spectra were recorded at 300 MHz in $CDCl_3$ for neutral compounds and in CD_3NO_2 solution for salts

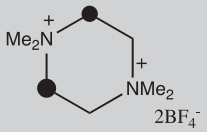
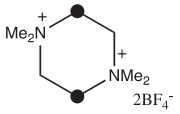
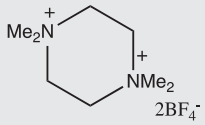
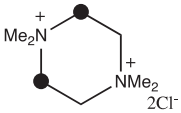
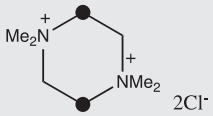
definitive, particularly in the fingerprint region of the IR spectrum that is diagnostic of the vibrational modes of the molecular structure as a whole. Aided by comparison of the product mixture **9a-** and **9b-d4-2BF4** with authentic labeled samples prepared by independent methods, we were able to determine the label distribution in **9-d4.**

Thus, lithium aluminum deuteride (LAD) reduction of 1,4-*N*,*N*-dimethyl-2,6-piperazinedione **7a** to give **8a** followed by methylation with 2 equivalents of trimethyloxonium fluroroborate gave **9a-d4-2BF4**, while the isomeric 2,5-piperazinedione **7b** on LAD reduction to **8b** and methylation gave **9b-d4-2BF4** (Scheme 3). (See Tables 1, 2, and 3 for chemical shift data and the prominent IR absorption frequencies). Note that the NMR spectra of **8a** and **8b** are indistinguishable. Figure 1 shows the IR spectra of **9a** and **9b** in the fingerprint region).

Because strong and broad IR absorption bands of the BF_4^- anion interfered with analysis of the IR region of interest in the labeled salt products, it was necessary to convert the fluoroborate double salts **9-2BF4** to the corresponding chloride salts by metathesis with KCl. IR analysis of the chloride double salts in KBr pellets revealed a fine pattern of distinctive absorption bands for each deuterated isomer in the fingerprint region (800-900 cm^{-1}). Careful comparison of related key absorption bands (frequencies and intensities) evident in the IRs of authentically labeled samples of **9a-d4-2Cl** and **9b-d4-2Cl** (Figure 1) with the labeled dimerization products **9-d4-2Cl** (Figure 1b) allowed for a reliable estimate of the label distribution. The results of this analysis revealed that the salt product **9-d4-2Cl** (formed from the dimerization of **3-d2-BF_4** and conversion to the corresponding chloride salt) was a mixture of **9a-d4-2Cl** and **9b-d4-2Cl** in *equal amounts*. That is so say, the IR absorption bands of the dimerization product could be closely reproduced from a 50:50 mixture of authentic samples of **9a-d4-2Cl** and **9b-d4-2Cl** (see Figure 1a and 1b). Furthermore, label shuffling in the reactant **3-d2** can be ruled out as a source of label rearrangement observed in the **9-d4** product mixture because *no label shuffling* in **3-d2** was observed under the reaction conditions. We conclude therefore that formation of mixtures of **9a-d4** and **9b-d4** as fluoroborates is plausible evidence of a reaction pathway involving the aziridium ion intermediate **4-d2-BF4** as summarized in Scheme 4 with the caveat that **4** must be formed *irreversibly* from **3**.

The mechanism in Scheme 4 appears to parallel that suggested by Bartlett et al in their related studies of piperazinium formation from dimethyl-(2-chloroethyl) amine **5**.[4] Indeed, we prepared the deuterium-labeled dimethyl-(2-chloroethyl)amine salt **5a-d2-HCl** by LAD reduction of ethyl *N*,*N*-dimethylaminoacetate to give *N*,*N*-dimethylaminoethanol-d2 followed by conversion to protonated *N*,*N*-dimethylamino-2-chloroethane-d2 **5a-d2-HCl** with thionyl chloride (see Supporting Information). When deprotonated in nitromethane at room temperature overnight, the incipient product **5** dimerized to the dichloride salt **9-d4-2Cl**. We identified the dichloride salt to be a 50:50 mixture of **9a-d4-2Cl** and **9b-d4-2Cl** by IR analysis and by comparison with the spectra of authentic samples (Figures 1a and 1b). The result is consistent

TABLE 3 IR absorbances of tetramethylpiperazinium salts (KBr pellet)

 **9a-d4·2BF4**	3010, 2970, **2236** (C-D stretching), 1484, 1411, **1305 1038(BF4), 958,** 954, 942, **885**, 858, **840,** 772 cm^{-1}
 **9b-d4·2BF4**	3011, 2970, **2238** (C-D stretching), 1618, 1478, 1326, 1300, 1038(BF4), 987, 942, 863, 807, 771 cm^{-1}
Dimer salt 9-d4-2BF4	3011, 2969, **2237** (C-D stretching), 1483, 1410, **1326,** 1305, 1032 (BF4), **985, 954, 942, 884, 863, 840,807**, 771 cm^{-1}
 **9-2BF4**	3011, 2967, 1618, 1483, 1467, 1439, 1410, 1390, 1318, 1231, 1200, 1132, 1136, 1061, 1022, 972, 921, 872, 718, 634 cm^{-1}
 **9a-d_4-2Cl**	3010, 2970, **2236** (C-D stretching), 1483, 1411, **1364, 1304, 1207, 1175, 1159, 1042, 1006, 984, 955, 924,** 885, 858, 840, 814, 746 cm^{-1}
 **9b-d_4-2Cl**	3011, 2970, **2237**(C-D), 1478, 1410, **1326, 1221, 1197, 1049, 1011, 987, 944, 863, 807** cm^{-1}
Dimer salt cl 9-d_4-2Cl	3011, 2969, **2236**(C-D), 1481, 1407, **1364, 1326, (1303,** 1256, **1221, 1197, 1175, 1158, 1042, 1006, 986, 954, 943, 885, 863, 839, 807** cm^{-1}

Bold numbers indicate the differences in absorbances as a result of deuterium labeling. Dimer salt data represent absorbances of product derived from the labeled precursors, **3-d2-BF34 fluoroborate salt or 5-d2**.

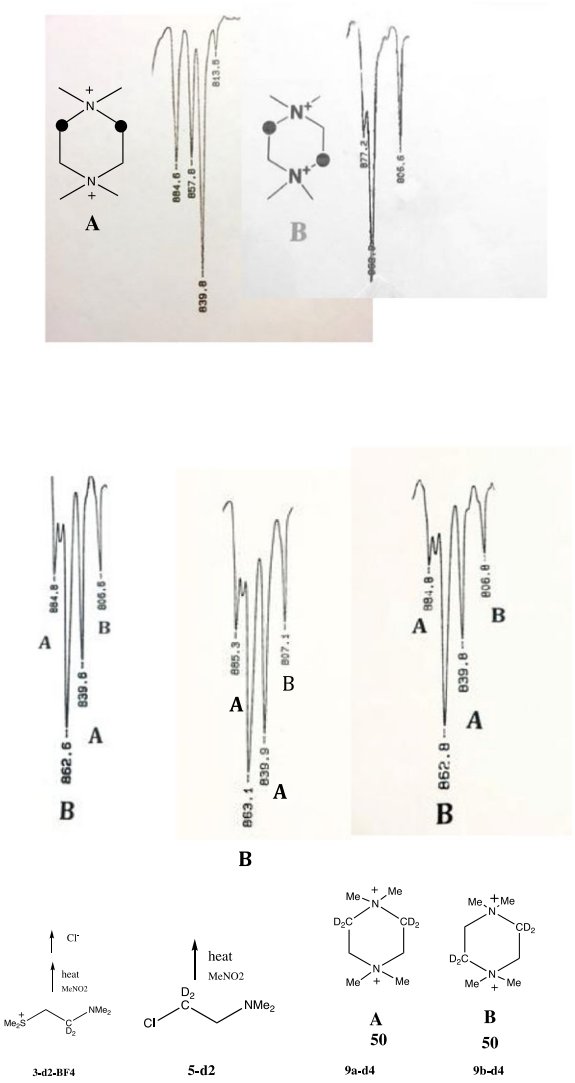


FIGURE 1 (A) TOP: IR absorbances 800 to 900 cm^{-1} of **A (9a-d4-2Cl)** 885, 858, 840; **B (9b-d4-2Cl)** 877, 863, 807; (B) BOTTOM: IR absorbances 800 to 900 cm^{-1} of product mixture (as dichloride double salts from heating **3-d2-BF4** (885, 864, 840, 806); **5-d2** (885, 863, 840. 807); and a 50:50 mixture of authentic **9a** and **9b-d4-2Cl** (885, 863, 840, 807)

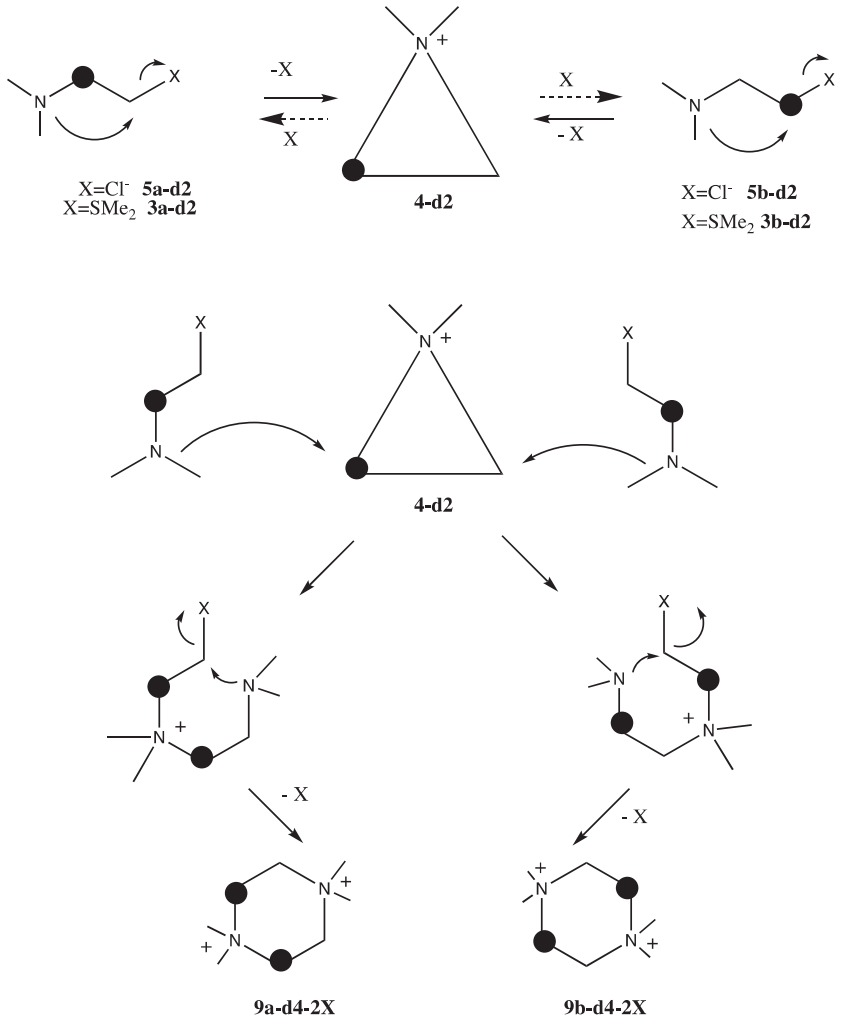
with the intervention of the symmetrical intermediate aziridium ion **4**. However, NMR analysis of recovered starting material **5** revealed that label rearrangement had also occurred, which suggests that, in this case, the aziridium intermediate **4** is formed *reversibly* from **5**.

7 | CONCLUSION

Heating (2-substituted)-ethylamines of the type $Me_2NCH_2CH_2X$ where the X substituent is a good leaving group (Cl^- in **5**, and SMe_2 in **3**) lead rapidly to elimination of X and formation of tetramethylpiperizinium salt **9**. Evidence from the deuterium labeling experiments support the intermediacy of dimethylaziridinium ion **4** in the formation of **9.**

The displacement step to form the aziridium intermediate **4** is a 3-exo-tet cyclization of the homoanomeric system n(N) → sigma*(C - X) known to be important for favorable cyclization kinetics.[9]

There is, however, a basic difference in the behavior of **4** depending on the nature of **X**. Apparently **4** is formed reversibly from **5** (**X = Cl**) but irreversibly from **3** (**X = Me_2S**). A likely explanation is that under aprotic solvent conditions, the aziridium intermediate from **5** is actually a tight ion pair that can readily return internally

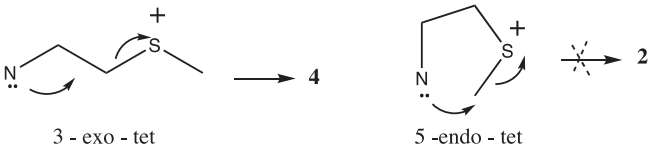


SCHEME 4 Aziridium Ion Intermediates in the Formation of Piperazinium Salts

before capture to give the dimeric product **9**. This would certainly explain label shuffling observed in both reactant and product. It is also consistent with the expectation that the nucleophilicity of the chloride anion is enhanced in aprotic solvents such as nitromethane or acetonitrile and would compete favorably for capture of **4** over an approaching amine nitrogen of **5** that would lead to the product **9**.

In contrast, in the case of **3**, the counter ion is non-nucleophilic ($BF4^{-}$), and a comparable ion-pair-internal return sequence involving **4** is not relevant. Because the deuterium label is shuffled only in the product, recapture of the aziridium intermediate **4** by the sulfide nucleophile Me_2S does not compete kinetically with capture of **4** by the amine nitrogen of **3** to form the product. These results are summarized in Scheme 4.

Finally, the behavior of the dimethylsulfonium salt **3** is worthy of further comment. There are 2 reactions of **3**, one leading to the double salt **9** via the aziridium ion **4** and the other to the isomeric ammonium salt **2**. In principle, both reactions could involve cyclization pathways, one via a 3-exo-tet path, the other by a 5-endo-tet path.



As noted, the results reported here are consistent with the known favorable kinetics of the 3-exo-tet process to give **4**. The alternative 5-endo-tet path to **2** is non-competitive kinetically and is disfavored for stereoelectronic reasons.[3,7] Nevertheless, **3** does rearrange to **2**, but not by the 5-endo-tet route. The actual pathway is not entirely clear and is slow compared with the kinetically favored transformation of **3** to **4**, but it demonstrates that **2** is thermodynamically more stable than **3**.

In summary, the behavior of structure **3** reveals reactions that illustrate both kinetic and thermodynamic nucleophilicity of nitrogen compared with sulfur. Thus,

nitrogen competes favorably with sulfur for the carbon electrophile in the thermodynamically controlled rearrangement of **3** to **2**. Also, nitrogen is apparently kinetically dominant over sulfur in a 3-exo-tet cyclization process, as evidenced by the facile elimination of Me_2S and formation of aziridium ion **4** on heating **3**. A comparable cyclization of the ammonium isomer **2** to eliminate Me_3N via an episulfonium intermediate was not observed. This is consistent with the reported favorable kinetics of homoanomeric n(X) → sigma*(C - Y) systems in a 3-exo-tet closure when the donor nucleophile X is nitrogen.[9]

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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