Nucleophilic Substitution on 4-Methylbenzyl Thiocyanate with Nucleophiles

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The reactions of 4-methylbenzyl thiocyanate (**1**) with several nucleophiles have been investigated. Compound **1** possesses three electrophilic sites, *i.e.*, benzylic carbon, sulfur and cyano carbon, to receive nucleophilic attack. PhS^- and CN^- which have HOMO's of high energy levels appear to attack preferentially the sulfur atom. MeO^- was found to attack preferably the cyanide carbon, while amines which have HOMO's of low energy levels prefer benzylic carbon to attack. The nucleophilic substitution on the sulfur or the cyanide carbon generates CN^- or *p*-xylene-α-thiolate anion, strong nucleophiles, as the primary products, which then initiate the complex secondary reactions. The selective reactivities of three attacking sites for nucleophiles in **1** have been rationalized in terms of MO theory.

The reactions between organic thiocyanates and nucleophiles are of interest, because organic thiocyanates possess three reacting sites for the nucleophilic attack, *i.e.*, the carbon linked to thiocyanato group (site a), the sulfur atom (site b), and the cyanide carbon atom (site c), (Fig. 1).[1,2] The reactions of organic thiocyanates with a few nucleophiles have been investigated mainly for synthetic interest to prepare thiols from thiocyanates.[3] Giles and Parker carried out mechanistic studies on the reaction between 2,4-dinitrophenyl thiocyanate and various nucleophiles in DMF.[2] They determined the rate constants for the reactions at the sites a, b, and c with various nucleophiles, and concluded that thiolate anion is the only nucleophile which attacked the sulfur atom (site b) among nucleophiles they used, *i.e.*, RS^-, CN^-, ArS^-, RO^-, ArO^-, SCN^-, N_3^-, amines, halide anions, and NO_2^-.

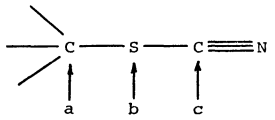


Fig. 1. Three possible sites for the reaction of organic thiocyanate with nucleophiles.

However, no systematic investigation on the reactions between alkyl thiocyanate and various nucleophiles has been reported. Thus, we have initiated the investigation of the reaction between alkyl thiocyanate and various nucleophiles. When the initial attack of nucleophile on 4-methylbenzyl thiocyanate (**1**) took place at the sites b and c, the reactions were found to be very complex because of various secondary reactions initiated by CN^- or $4\text{-}CH_3C_6H_4CH_2S^-$ (**6**) which were generated by the initial nucleophilic displacements at the sites b and c of **1**, respectively. On the other hand, no such secondary reaction was observed, when the initial reaction proceeded at the site a, which produced SCN^-, a relatively weak nucleophile. In order to characterize the leaving ability of thiocyanate upon nucleophilic substitution as a pseudo-halogen, rate constants of the reaction between **1** and 4-methylbenzyl halides and 1,4-diazabicyclo[2.2.2]-octane (DABCO) were measured in an aprotic solvent, *i.e.*, acetonitrile since the nucleophilic attack by DABCO has been found to take place exclusively at the site a.

The nucleophiles used in this work and all possible reaction products with these nucleophiles are listed in Table 1.

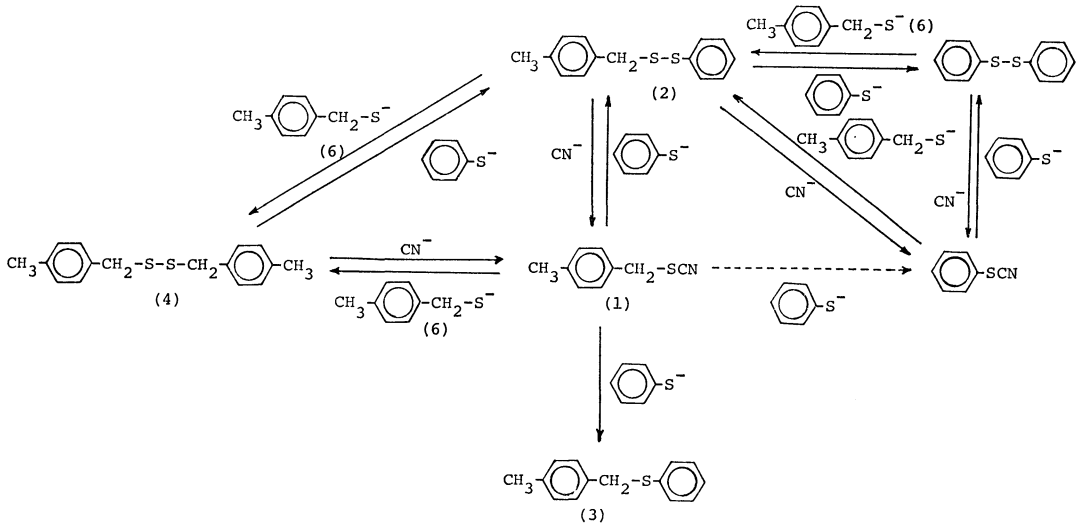
Results and Discussion

4-Methylbenzyl thiocyanate (**1**) was chosen as the substrate for this purpose since it has no α-hydrogen atom to initiate the base catalyzed elimination of hydrogen thiocyanate forming olefin and it is convenient to analyze reaction products by the NMR method.

Reaction with Potassium Benzenethiolate in Methanol. The reaction of **1** with potassium benzenethiolate was conducted in methanol at room temperature and followed by GLPC. The starting material **1** was found to disappear immediately, generating 4-methylbenzyl phenyl disulfide (**2**) as the major product along with minor products, *i.e.*, diphenyl disulfide and bis(4-methylbenzyl) disulfide (**4**). Then, three disulfides were gradually converted to 4-methylbenzyl phenyl sulfide (**3**) as shown in Fig. 2. After 2 d at room temperature, **3** was obtained eventually as the sole product (90% isolated yield). This may be rationalized by the mechanism illustrated in Scheme 1. Initial formation of a large amount of the unsymmetrical disulfide **2** as the primary product suggests that the initial

TABLE 1. ALL POSSIBLE REACTION PRODUCTS IN THE REACTIONS OF RSCN WITH NUCLEOPHILES

Nucleophile	Reaction site		
	a	b	c
PhS^-	$R\text{-}SPh + SCN^-$	$RS\text{-}SPh + CN^-$	$PhS\text{-}CN + RS^-$
CN^-	$R\text{-}CN + SCN^-$	$RS\text{-}CN + CN^-$	$NC\text{-}CN + RS^-$
MeO^-	$R\text{-}OMe + SCN^-$	$RS\text{-}OMe + CN^-$	$MeO\text{-}CN + RS^-$
R'_3N	$R\text{-}{}^+NR'_3 + SCN^-$	$RS\text{-}{}^+NR'_3 + CN^-$	$R'_3N^+\text{-}CN + RS^-$
N_3^-	$R\text{-}N_3 + SCN^-$	$RS\text{-}N_3 + CN^-$	$N_3\text{-}CN + RS^-$



Scheme 1. Possible reaction paths for the reaction of **1** with potassium benzenethiolate.

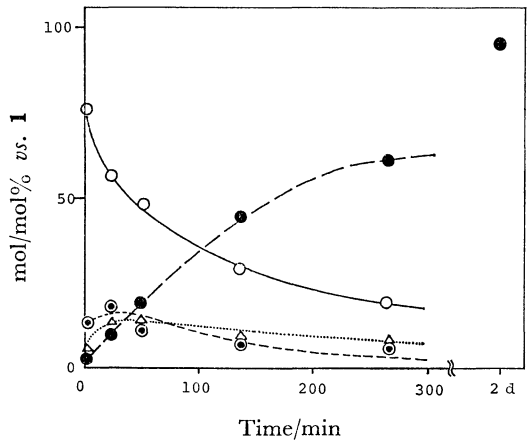


Fig. 2. The reaction of **1** (1.05 mmol) with potassium benzenethiolate (1.24 mmol) in methanol (3 ml) at 25 °C.
○: **2**, ●: **3**, △: **4**, ⊙: diphenyl disulfide.

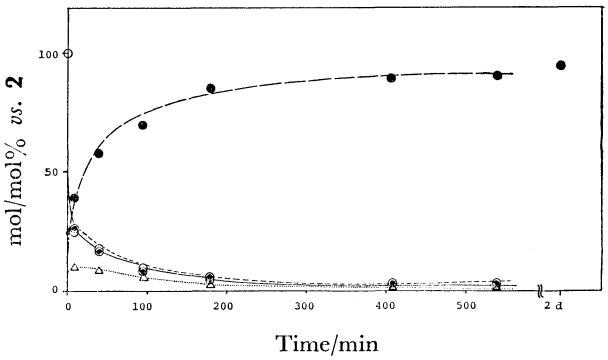


Fig. 3. The reaction of **2** (0.459 mmol) with equimolar amount of sodium cyanide in acetonitrile (5 ml) in the presence of 18-crown-6 (0.114 mmol) at 25 °C.
○: **2**, ●: **3**, △: **4**, ⊙: diphenyl disulfide.

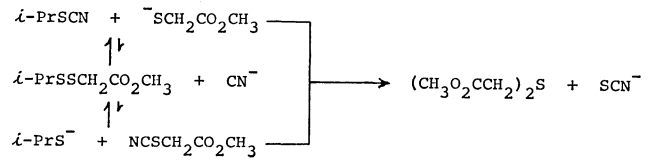
attack of benzenethiolate anion toward **1** takes place mainly on the sulfur atom of **1** (site b) in keeping with the precept that the thiolate anion is an excellent nucleophile toward divalent sulfur,[4] while the reaction at the site a took place very slowly forming **3** irreversibly. However, since cyanide anion, one of the primary product of the reaction at the site b with benzenethiolate anion, has a strong thiophilicity toward divalent sulfur,[4,5] the reaction of the unsymmetrical disulfide **2** with cyanide anion (CN^-) reproduces the staring **1** or generates phenyl thiocyanate depending on the attacking sites of two sulfur atoms of **2**. The unsymmetrical disulfide **2** gives the symmetrical disulfide **4** by the reaction with *p*-xylene-α-thiolate anion (**6**), while the reaction with benzenethiolate anion forms diphenyl disulfide which may react with CN^- to result phenyl thiocyanate. Phenyl thiocyanate reproduces the disulfide **2** and diphenyl disulfide by the reaction with **6** and benzenethiolate anion (PhS^-), respectively.

The control experiment showed, in fact, that the reaction of phenyl thiocyanate with **6** took place immediately to give the same products distribution as the reaction between **1** and PhS^-. The reaction of **1** with **6** (site b) also generates the symmetrical disulfide **4**, which reproduces either **1** upon the reverse reaction with CN^- or **2** by the reaction with PhS^-. In fact, treatment of the symmetrical disulfide **4** with CN^- in a separate experiment gave bis(4-methylbenzyl) sulfide **5** which was produced undoubtedly *via* **1**. Absence of **5** in the final reaction mixture of the reaction of **1** with PhS^- is due to that the steady concentration of the thiolate anion **6** is too small to compare with that of PhS^- during the reaction. Thus, the unsymmetrical sulfide **3** is gradually formed as the final product through the irreversible reaction at the site a of **1** which is regenerated through the reversible reactions, as shown in Scheme 1.

The sequence of the secondary reactions which start from the unsymmetrical disulfide **2** by action of CN^- and thiolate anions have been substantiated by the following control experiment. The reaction between sodium cyanide and the disulfide **2** under the same conditions which have been applied for the reaction of **1** with potassium benzenethiolate, gave the mixture of same products and followed the kinetic course shown in Fig. 3 as the reaction between **1** and potas-

sium benzenethiolate did; *i.e.*, Fig. 3 is roughly identical to Fig. 2.

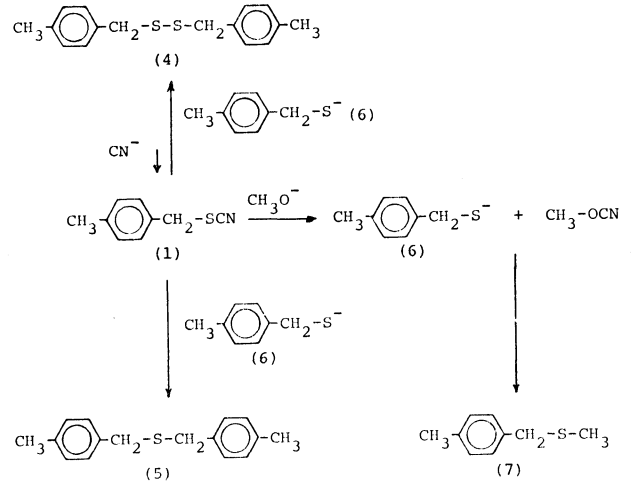
The consequence of this rapid equilibration among two thiocyanates and two disulfides which are promoted by both CN^- and the thiolate anions is well consistent with the result of Harpp *et al.* who observed that CN^- catalyzed S–S bond fission of unsymmetrical disulfide forms the following equilibrium and eventually affords the symmetrical sulfide (Scheme 2).[5]



Scheme 2. Cyanide cleavage of unsymmetrical disulfide.

The rate ratio of the reactions at the site a forming **3** *vs.* that at the site c to afford thiocyanate for the reaction of **1** with PhS^- may be greater than that of the reaction at the site a *vs.* that of the site e for the reaction of 2,4-dinitrophenyl thiocyanate with thiolate anion, because the leaving ability of 2,4-dinitrobenzenethiolate must be much better than that of **6**. Therefore, the fact that the reaction at the site a is 10^3 folds faster than that at the site c in the reaction of 2,4-dinitrophenyl thiocyanate with PhS^- may suggest that the reaction at the site c in the reaction of **1** with PhS^- is less important than that at the site a.

Reaction with Sodium Methoxide in Methanol. The reaction between **1** and sodium methoxide in methanol was completed within a minute at room temperature under argon. The symmetrical disulfide **4** was obtained as the major product (89% isolated yield). Any 4-methylbenzyl methyl ether which is expected to be produced by the reaction at the site a was not detected by GLPC analysis of the reaction mixture, however, a small amount of 4-methylbenzyl methyl sulfide (**7**) was found to be formed (3% isolated yield). The possible mechanism is shown in Scheme 3. The initial reaction may be the nucle-



Scheme 3. Possible reaction paths for the reaction of **1** with sodium methoxide.

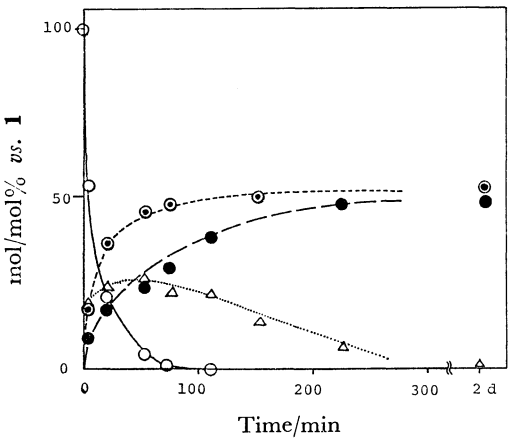
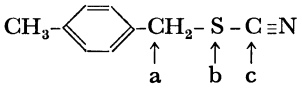


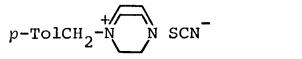
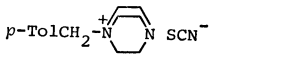
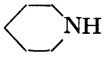
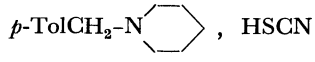
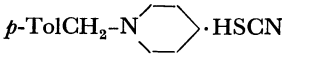
Fig. 4. The reaction of **1** (0.650 mmol) with sodium cyanide (2.5 mmol) in the presence of 18-crown-6 (0.49 mmol) in refluxing acetonitrile (14 ml).
○: **1**, △: **4**, ⊙: **5**, ●: **8**.

ophilic attack of methoxide anion (MeO^-) on the cyanide carbon (site c) of **1** to give the thiolate anion **6** and methyl cyanate. Failure of detection of methyl cyanate may be due to its instability even at room temperature[6] and its easy consumption by the reaction with the thiolate anion **6**. Since a thiolate anion behaves usually as a much stronger nucleophile than MeO^- in protic solvents, the secondary reaction between **1** and **6** proceeded more rapidly than the primary reaction, after once the thiolate anion **6** was formed by the primary reaction between **1** and MeO^-. There are two possible paths to consume **6**, a very strong nucleophile, thus formed. One is the reaction with **1** to afford **4**. The other is the reaction with methyl cyanate to form the sulfide **7**.[7] Product yields suggest that the former path predominates over the latter path. Since the reaction was conducted under argon, the disulfide **4** was undoubtedly formed by the reaction promoted by the thiolate anion **6** formed as a primary reaction product but not formed by the oxidation of thiolate anion **6** with molecular oxygen as assumed by Parker and Giles in their work on aryl thiocyanates.[2] CN^- is also known to be a rather strong nucleophile especially towards a divalent sulfur, however, much weaker nucleophile than the thiolate anion **6**.[4] Therefore, the reaction of **1** with MeO^- was intercepted by **6** before the complex reactions of the disulfide **4** were promoted by CN^-.

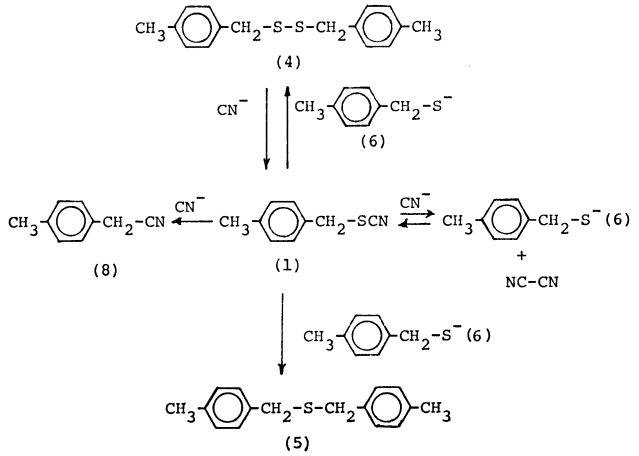
Reaction with Sodium Cyanide in Acetonitrile. The reaction of **1** with sodium cyanide was carried out in the presence of 18-crown-6 ether as the phase transfer catalyst in refluxing acetonitrile under argon. The reaction was monitored by GLPC and the result is illustrated in Fig. 4. Inspection of the figure reveals that a substantial amount of the disulfide **4** is produced at the initial stage and then converted to 4-methylbenzyl cyanide (**8**), and bis(4-methylbenzyl) sulfide (**5**) by subsequent reaction with CN^- as shown in Scheme 4 as Harpp observed in the reaction between CN^- and unsymmetrical disulfide (Scheme 2).[5] As illustrated in Scheme 4, CN^- attacks concurrently the benzyl carbon atom (site a) and the cyanide carbon atom

Table 2. Reaction sites of **1** toward nucleophiles



Nucleophile	Solvent	Temp	Time	Attacking site	Initial product	Final product
	MeCN	r. t.	5 h	a		
	MeCN	r. t.	28 h	a		
Et_2NH	MeCN	r. t.	48 h	a	p-$TolCH_2$-NEt_2·HSCN	p-$TolCH_2NEt_2$·HSCN
N_3^- [a]	MeCN	refl.	20 min	a	p-$TolCH_2$-N_3	p-$TolCH_2$-N_3
PhS^- [b]	MeOH	r. t.	fast	b > a	p-$TolCH_2S$-SPh	p-$TolCH_2$-SPh
CN^- [c]	MeCN	refl.	3 h	b > c > a	p-$TolCH_2S$-*CN p-$TolCH_2$-CN, p-$TolCH_2S^-$	p-$TolCH_2SCH_2Tol$-p p-$TolCH_2$-CN
MeO^- [d]	MeOH	r. t.	fast	c	p-$TolCH_2S^-$, MeO-CN	p-$TolCH_2SCH_2Tol$-p, p-$TolCH_2SMe$

a) NaN_3/18-crown-6. b) PhSK. c) NaCN/18-crown-6. d) MeONa.



Scheme 4. Possible paths for the reaction of **1** with sodium cyanide.

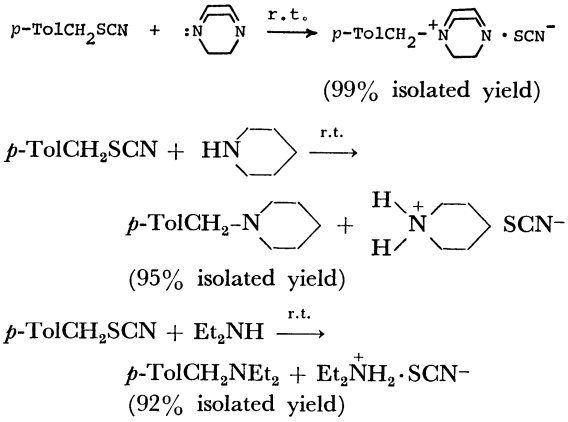
site C of **1** to generate **8**, and **6** and cyanogen, respectively. The thiolate anion **6** thus formed reacts readily with **1** to give **4** and slowly to give the sulfide **5**. The disulfide **4** may be converted to **5** and **8** *via* forming **1**.

Meanwhile, the nucleophilic displacement of cyano group of alkyl thiocyanates with radioactive cyanide anion ($*CN^-$) was known to proceed even at room temperature.[8] Therefore, in the reaction of **1** with CN^-, the reaction at the site b, *i.e.*, cyanide exchange reaction, is concluded to be the fastest,[8] then the reaction at the site c to form **6** and the reaction at the site a affording **8** is the slowest.

$$RSCN + *CN^- \xrightarrow{25\,^\circ C \text{ in MeOH}} RS*CN + CN^-$$

R = Me, Et, *i*-Pr, *t*-Bu, Benzyl, and Phenyl

Reactions with Amine Nucleophiles in Acetonitrile. Both secondary and tertiary aliphatic amines were found to attack exclusively benzyl carbon of **1** (site a) at room temperature (Menschutkin reaction) as follows.[9] The reaction products were identified by IR and NMR spectroscopic analyses, and elemental analysis.



Reaction with Sodium Azide in Acetonitrile. The reaction between **1** and azide anion gave slowly 4-methylbenzyl azide (site a) in 95% isolated yield.

$$p\text{-}TolCH_2SCN + NaN_3 \xrightarrow{\text{reflux}} p\text{-}TolCH_2N_3 + NaSCN$$

*Reaction Site of **1** with Nucleophiles.* As mentioned earlier, the actual reacting site among the three reacting sites of **1** varies with the reacting nucleophile. Table 2 summarizes the preference of the reacting site in the actual reaction of **1** with each nucleophile. Since MeO^- attacks preferentially the site c, the cyanide carbon of **1** is the hardest electrophilic center, while the different reactivities of these nucleophilic reagents toward these three different reacting sites have been explained qualitatively in terms of the HSAB principle.[10] The softest reacting site for the nucleophile is the sulfur atom (site b), while the hardest one is the cyanide carbon atom (site c). In keeping with the HSAB principle, the softest nucleophile, PhS^-, is so thiophilic that it attacks preferentially the site b and even soft CN^- preferentially attacks the site b. Amines and N_3^-, being relatively hard but not very thiophilic, attack the site a. The results of INDO MO calculation are also in a good agreement with those conclusion.

*Theoretical Consideration of Reactivity of **1**.* The

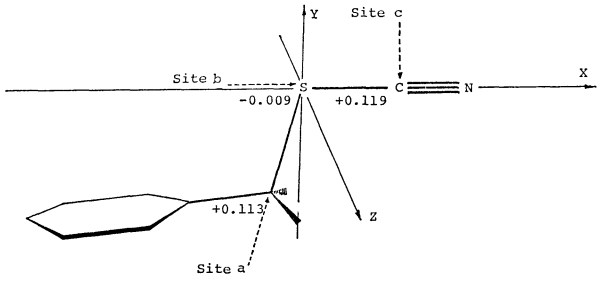


Fig. 5. Geometry of benzyl thiocyanate to be used for the MO calculation, net charge of benzyl thiocyanate and the course of the nucleophilic substitution through the sites a, b, and c.

Table 3. Net-charge on the nucleophilic atom and the HOMO orbital energy of nucleophiles

Nucleophile	Net-charge on the nucleophilic atom	HOMO energy eV
PhS^-	−0.748	−1.84
N_3^-	−0.712	+0.25
MeO^-	−0.694	−1.70
CN^-	−0.576	−0.28
DABCO	−0.184	−10.29

observed preferential sites for nucleophilic attack with different nucleophiles (Table 1) can be compared with the results of the INDO MO calculations.[11] The interaction energy between the nucleophile and the electrophile may be divided in the following two terms, *i.e.*, the electrostatic interaction and orbital interaction.[12] The calculated charge distribution of benzyl thiocyanate is shown in Fig. 5†. The net charges on the nucleophilic atoms of the nucleophiles are listed in Table 3. The calculated orbital interaction energies for the three reaction sites of benzyl thiocyanate toward the various nucleophiles are listed in Table 4. The net-charges on the benzyl carbon atom (site a) and the cyanide carbon atom (site c) are positive. On the other hand, the charge density on the sulfur atom (site b) is very small. The orbital interaction is the largest on the sulfur atom. Thus, the calculation suggests that the charge interaction is important in the reactions at the sites a and c, while the orbital interaction is predominant for the reaction at the site b. This prediction is well consistent with the present experimental results, *i.e.*, the PhS^-, which is a typical soft nucleophile[10] and is expected to undergo the orbital-controlled reaction,[12] attacks indeed the sulfur atom, while the MeO^-, which is a typical hard nucleophile[10] and is expected to undergo the charge-controlled reaction,[12] reacts at the positive carbon atom.

As may be seen from Table 4, the orbital interactrons of PhS^- and CN^- are very large. Their largest orbital interactions at the site b are due to the electron transfer from the nucleophiles to the 28th MO of benzyl thiocyanate. As is shown in Fig. 6, the 28th MO of benzyl thiocyanate has a strong anti-

† MO calculation of benzyl thiocyanate has been carried out instead of **1** to simplify the system.

Table 4. Orbital interaction of three reaction sites of benzyl thiocyanate toward various nucleophiles[a]

Nucleophile	Site a	Site b	Site c
PhS^-	−208	−284	−148
CN^-	−170	−236	−111
N_3^-	−119	−170	−73
MeO^-	−77	−131	−57
DABCO	−16	−30	−15

a) Values are in unit of $10^{-5}\times(\beta_0)^2$, where $\beta_{rs}=S_{rs}\beta_0$. For the calculation procedure, see the experimental part.

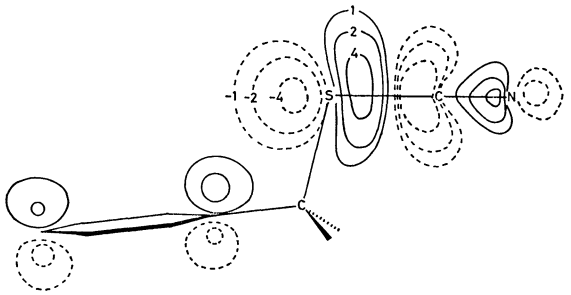
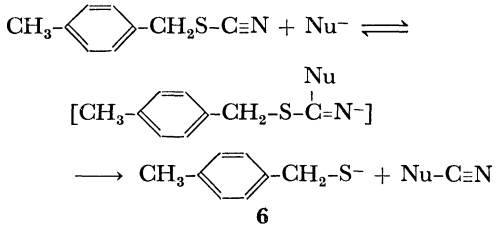


Fig. 6. 28th MO map of benzyl thiocyanate.

bonding character between the S–CN bond, and the electron transfer from a nucleophile (X^-) to this orbital weakens the S–CN bond and causes eventually the bond breaking to give the reaction products, $PhCH_2X$ and CN^- (X=PhS, *CN). The PhS^- and CN^- are thus expected to react at the site b preferentially through the orbital interaction. Since the calculated orbital interaction energies of MeO^- and amines are quite small, they are expected to attack the positive carbon atom of benzyl thiocyanate by the charge interaction. However, the prediction of the preferential reaction sites, a or c, is difficult, because of the following reasons, namely, the mechanism of the reaction at the sites, a and c, are different from each other and any molecular and electronic structural changes during the reaction process were not taken into account in the present calculation. The reaction at the site c may proceed through the following addition-elimination process[13] in which the second step of the reaction can take place only when the nucleophile is MeO^- among several nucleophiles used in this work, since the thiolate anion **6** is a much better leaving group than MeO^-.



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Since the reaction at the site a involves the inversion of the sp^3 carbon atom, it requires an appreciable activation energy and hence the reaction of amines at the site a proceeds slowly.

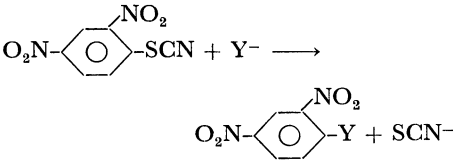
The calculated orbital interaction energies of N_3^-

(Table 3) suggests that N_3^- may react on the sulfur atom of **1** to give *p*-TolCH$_2$–S–N=$\overset{+}{N}$=$\overset{-}{N}$, although the formation of *p*-TolCH$_2$SN$_3$ was not detected in the experiment, and only the product which is produced *via* the reaction at the site a was observed experimentally. Since N_3^- is a very good leaving group, *p*-TolCH$_2$SN$_3$ if formed may undergo very fast reverse reaction with CN^-, a strong nucleophile, to regenerate **1** and N_3^-. However, this was unable to be confirmed in the present experiment.

$$p\text{-TolCH}_2\text{-S-C}\equiv\text{N} + N_3^- \rightleftarrows p\text{-TolCH}_2\text{-S-N=}\overset{+}{\text{N}}\text{=}\overset{-}{\text{N}} + CN^-$$

1

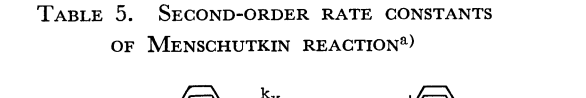
Leaving Ability of Thiocyanate Anion. Thiocyanate anion has been characterized as a pseudo halogen. It is ranked between iodide and chloride in the nucleophilic order of halide anions: $I^->SCN^->Br^->N_3^->Cl^->F^-$ in the reaction in protic solvents.[14,15] Nucleophilic order of halides observed in protic solvents is just opposite to that in aprotic solvents and thiocyanate becomes the worst nucleophile toward methyl tosylate in DMF: $F^->Cl^->Br^->SCN^-$, while the following nucleophilic order $F^->Cl^->SCN^->Br^->I^-$ was reported in the nucleophilic substitution of SCN group of 2,4-dinitrophenyl thiocyanate in DMF.[2] Meanwhile the leaving ability of thiocyanate in the nucleophilic substitution on sp^3 hybridized carbon has not yet been compared with other halides, while the following leaving abilities in the nucleophilic substitution was reported by Giles and Parker.[2]



Leaving ability: $Br^->I^->SCN^->Cl^->F^-$ in DMF

Thus rate constants for the Menschutkin reactions of 4-methylbenzyl thiocyanate, chloride, and bromide have been measured in acetonitrile at 28±0.05 °C using DABCO as the choice nucleophile, since it has been found to attack the site a of **1** exclusively. The kinetic measurement has been carried out by following the increase of conductivity of the reaction mixture due to the formation of quarternary ammonium salt. The reaction was found to be of first order in both **1** and DABCO. The results are shown in Table 5.

Table 5. Second-order rate constants of Menschutkin reaction[a]



k_{Br}/l mol^{-1} s^{-1}	7.29
k_{Cl}/l mol^{-1} s^{-1}	0.0559
k_{SCN}/l mol^{-1} s^{-1}	0.00328

a) In CH_3CN at 28±0.05 °C.

The rate ratio, $k_{Br}/k_{Cl}=130$, observed in this work is same order as those which have been usually observed in S_N2 reaction on sp^3 carbon (50—180).[16] pK_a Values of the conjugate acid (HX) of the leaving anion (X^-) may be taken as one of criteria for the leaving ability of X. The observed rates, $k_{SCN}:k_{Cl}:k_{Br}=1:17:2200$, is in accordance with pK_a values of HSCN (−1.85), HCl (−6.1), and HBr (−9).[17]

Experimental

All melting points are uncorrected and were taken on Yanaco melting-point apparatus. The IR spectra were obtained on Hitachi 260-50 infrared spectrophotometer and the NMR spectra with Perkin-Elmer Hitachi R-20 (60 MHz) spectrometer. GC-Mass spectra were determined with Hitachi RMU 6MG GC-MS spectrometer equipped with 3 mm×2 m glass column of 15% Silicone OV-1 on Chromosorb W. All the reactions were monitored by the chromatography, namely, TLC (Merck, Kieselgel 60-GF$_{254}$), GLPC (Shimadzu GC-6A or Hitachi 163, using a 7—10% OV-1 on 60—80 mesh Chromosorb W. in 3 mm×2 m glass column), HPLC (Hitachi 638-50).

Materials. Acetonitrile was refluxed over phosphorus pentoxide for 30 h and distilled: bp 82.6 °C/760 mmHg†† Methanol was dehydrated by refluxing with magnessium and distilled: bp 64.0 °C/760 mmHg. Other reagents were obtained from Wako Pure Chemical Industries, Ltd. or Tokyo Kasei Co. Ltd., commercially.

4-Methylbenzyl Thiocyanate (***1***) was prepared by treatment of 4-methylbenzyl chloride with potassium thiocyanate, as follows. A mixture of 5.0 g (0.03 mol) of *p*-methylbenzyl chloride and 5.0 g (0.05 mol) of potassium thiocyanate in 30 ml of 90% ethanol was refluxed for 20 h, diluted with 120 ml of water, extracted three times with 20 ml aliquots of chloroform. The chloroform solution was washed with water, dried over Na_2SO_4 and evaporated to obtain crude 4-methylbenzyl thiocyanate whose GLPC analysis showed the presence of a small amount of 4-methylbenzyl isothiocyanate. 4-Methylbenzyl thiocyanate was separated from the impurities by elution column chlomatography (Merck, Kieselgel 60; eluent: 1:1 benzene–hexane); yield 58%; IR (neat) 2160, 1510, 1250, 820, 720 and 640 cm^{-1}; NMR ($CDCl_3$) δ=2.40 (3H, s, CH_3–), 4.14 (2H, s, –CH_2–) and 7.20 (4H, s, –C_6H_4–).

Found: C, 66.14; H, 5.52; N, 8.79%. Calcd for C_9H_9NS: C, 66.22; H, 5.55; N, 8.58%.

Potassium Benzenethiolate was prepared by dissolving benzenethiol in 2% solution of potassium methoxide in methanol, condensed to dryness under reduced pressure, washed with dry benzene, dried under vacuum and stored in a desiccator.

p-Xylene-α-thiol was prepared by the method reported by Frank and Smith[18] in 63% yield: Colorless oil; bp 110 °C/26.5 mmHg; (lit,[19] 116—118 °C/35 mmHg).

Bis(4-Methylbenzyl) Disulfide (***4***) was prepared by oxidation of *p*-xylene-α-thiol by iodine in 70% yield: Colorless crystals; mp 48.5—50.0 °C (lit,[20] 43 °C); IR (KBr) 1510, 1420, 1205, 820, 720 and 530 cm^{-1}; NMR ($CDCl_3$) δ=2.30 (6H, s, CH_3–), 3.57 (4H, s, –CH_2–) and 7.08 (8H, s, –C_6H_4–).

Bis(4-Methylbenzyl) Sulfide (***5***) was obtained by treating *p*-xylene-α-thiolate with 4-methylbenzyl chloride in ethanol in 90% yield, after recrystallization from ethanol: Colorless crystals; mp 78—79 °C (lit,[21] 76 °C); IR (KBr) 1510, 1420, 1110, 820, 730, and 530 cm^{-1}; NMR ($CDCl_3$) δ=2.36 (6H, s, CH_3–), 3.59 (4H, s, –CH_2–) and 7.12 (8H, s, –C_6H_4–).

4-Methylbenzyl Phenyl Disulfide (***2***). Benzenesulfenyl chloride was prepared by treating diphenyl disulfide with

†† 1 mmHg≈133.3 Pa.

chlorine gas[22] and was purified by vacuum distillation (43.5—44.5 °C/2 mmHg): yield 70%. The disulfide **2** could not be prepared by the method which has been applied for the preparation of other unsymmetrical disulfides by Parker and Kharasch,[4b] but synthesized successfully by the following method. To a solution of benzenesulfenyl chloride 1.05 g (7.25 mmol) dissolved in 10 ml of dry hexane containing dry pyridine was added at −10 °C. Into the mixture, 1.00 g (7.25 mmol) of *p*-xylene-α-thiol was added slowly in dark at −20 °C. The reaction was soon completed and the mixture was washed by water, and then with 5% H_2SO_4 (30 ml). The hexane solution was washed with water again, dried over $MgSO_4$ and evaporated. These must be operated in a dark room to avoid photochemical disproportionation of the unsymmetrical disulfide obtained. The residue was dried with vacuum pump (2 mmHg) for 4 h: Colorless oil; NMR ($CDCl_3$) δ=2.25 (3H, s, CH_3–), 3.82 (2H, s, $-CH_2-$), 6.80—7.60 (9H, m, $-C_6H_4-$ and $-C_6H_5$).

4-Methylbenzyl Phenyl Sulfide (3) was prepared by the same procedure which was applied for the preparation of **5** in 86% yield after recrystallization from ethanol: Colorless crystals; mp 69.0—70.1 °C (lit,[23] 69—70 °C); IR (KBr) 1580, 1510, 1480, 1440, 740, 690, and 480 cm^{-1}; NMR ($CDCl_3$) δ=2.27 (3H, s, CH_3–), 4.00 (2H, s, $-CH_2-$), 7.02 (4H, s, $-C_6H_4-$), and 7.15 (5H, s, C_6H_5–).

1-(4-Methylbenzyl)-4-aza-1-azoniabicyclo[2.2.2]octane Bromide, Chloride and Thiocyanate used for the kinetic study were prepared by the following method. 4-Methylbenzyl halide (0.013 mol) was added into the solution of 0.015 mol of DABCO in 50 ml of dry benzene at room temperature. After 30 min, benzene was evaporated and the residue, a white solid, was recrystallized from acetone–ether.

1-(4-Methylbenzyl)-1,4-Diazoniabicyclo[2.2.2]octane Bromide. 90% yield; Colorless crystals; mp 194.1—196.5 °C; IR (KBr) 2960, 1470, 1060, 820, 600, and 490 cm^{-1}; NMR ($CDCl_3$) δ=2.30 (3H, s, CH_3–), 3.10 (6H, t, J=8 Hz, DABCO), 3.71 (6H, t, J=8 Hz, DABCO), 4.86 (2H, s, $-CH_2-$), 7.01 (2H, d, J=8 Hz, $-C_6H_4-$), and 7.36 (2H, d, J=8 Hz, $-C_6H_4-$).

1-(4-Methylbenzyl)-1,4-Diazoniabicyclo[2.2.2]octane Chloride. 90% yield; Colorless crystals; mp 190.5—193.0 °C; IR (KBr) 2970, 1470, 1060, 820, 600, and 510 cm^{-1}; NMR δ=2.30 (3H, s, CH_3–), 3.07 (6H, t, J=8 Hz, DABCO), 3.69 (6H, t, J=8 Hz, DABCO), 4.86 (2H, s, $-CH_2-$), 6.98 (2H, d, J=8 Hz, $-C_6H_4-$), and 7.35 (2H, d, J=8 Hz, $-C_6H_4-$).

4-Methylbenzyl Cyanide (8) was prepared according to the method reported by Zubrik, Dunbar and Durst[24] in 51% yield after distillation: Colorless oil; bp 84.5 °C/30 mmHg (lit,[25] 220 °C/760 mmHg); IR (neat) 2250, 1515, 1415, 1120, 800, 750, 725, and 480 cm^{-1}; NMR ($CDCl_3$) δ=2.37 (3H, s, CH_3–), 3.67 (2H, s, $-CH_2-$), and 7.18 (4H, s, $-C_6H_4-$).

4-Methylbenzyl Methyl Sulfide (7) was prepared by the alkylation of sodium methoxide with 4-methylbenzyl chloride in 81% yield after distillation: Colorless oil; bp 121 °C/30 mmHg; IR (neat) 1520, 1425, 1240, 1110, 820, 735, 670, 525, and 470 cm^{-1}; NMR ($CDCl_3$) δ=1.94 (3H, s, CH_3-S-), 2.28 (3H, s, CH_3–), 3.56 (2H, s, $-CH_2-$), and 7.02 (4H, s, $-C_6H_4-$).

Reaction of 1 with Potassium Benzenethiolate. 171.0 mg (1.05 mmol) of **1** was added into a 3 ml of dry methanol solution containing 163.4 mg (1.24 mmol) of potassium benzenethiolate. The mixture was allowed to stand in argon atmosphere at room temperature monitoring by GLPC. Products, **2**, **3**, **4**, and diphenyl disulfide were obtained, and were identified by direct comparison with those of authentic samples by GLPC and GC-MS. **2**: (*m/e*) 246 (M^+), 105 ($4\text{-}CH_3C_6H_4CH_2^+$). **3**: (*m/e*) 214 ($M^+$), 105 ($4\text{-}CH_3C_6H_4CH_2^+$). Diphenyl Disulfide: (*m/e*) 218 (M^+), 109 (PhS^+).

Reaction of 4 with Sodium Cyanide. The disulfide **4** (123.1 mg, 0.449 mmol) was added into 5 ml of acetonitrile containing 50.6 mg (1.033 mmol) of sodium cyanide and 297.9 mg (1.128 mmol) of 18-crown-6. The mixture was stirred under reflux in argon atmosphere, the reaction being monitored by GLPC from time to time. The reaction completed in about 20 min. Then **5** and **8** were obtained by GLPC as final products. The same result was obtained when methanol was used as the solvent.

Reaction of Phenyl Thiocyanate with Sodium p-Xylene-α-thiolate. Sodium *p*-xylene-α-thiolate (160 mg, 0.685 mmol) prepared in the same procedure that was applied for the preparation of potassium benzenethiolate, was dissolved in 3 ml of abs. methanol and was added into the solution of phenyl thiocyanate (126.1 mg, 0.933 mmol; prepared by the usual way) at once. The mixture was allowed to stand at room temperature in argon atmosphere, while the reaction was monitored by GLPC at time intervals. Phenyl thiocyanate disappeared within 1 min and the gas liquid chromatogram of the reaction mixture showed the same distribution of products as in the reaction of **1** with potassium benzenethiolate, *i.e.*, initially, **2** was formed, and then disproportionated to **4** and diphenyl disulfide; eventually **3** was obtained as the final product.

Reaction of 2 with Sodium Cyanide. 113.2 mg (0.459 mmol) of **2** was added into a mixture of 24.1 mg (0.492 mmol) of sodium cyanide suspended in 5 ml of acetonitrile containing 30 mg (0.114 mmol) of 18-crown-6 and 56.3 mg (0.366 mmol) of biphenyl which was used as the internal standard on GLPC monitoring. The mixture was stirred in argon atmosphere at room temperature in dark. Figure 3 represents a rough kinetic picture of the reaction.

Reaction of 1 with Sodium Methoxide. Into a solution of sodium methoxide prepared by dissolving 67.8 mg (2.95 mmol) of sodium in 5 ml of absolute methanol, 176.2 mg (1.08 mmol) of **1** was added at once. The mixture was allowed to stand under argon atmosphere at room temperature monitoring by TLC. The reaction completed after 5 min. The remaining sodium methoxide was quenched by adding aqueous acetic acid solution. The mixture was extracted with chloroform twice. The chloroform extracts were combined, washed with water, dried over anhydrous magnesium sulfate and evaporated to afford a mixture of **4** and **7**. The two compounds were separated by silica gel column chlomatography with hexane as eluent. Compound **4** was eluted first (88.9% yield) and then **7** came out (2.2% yield).

Reaction of 1 with Sodium Cyanide. 106.0 mg (0.650 mmol) of **1** was added into a mixture of 121.1 mg (2.50 mmol) of sodium cyanide suspended in 14 ml of acetonitrile which contained 28.9 mg (0.490 mmol) of 18-crown-6. The mixture was refluxed under stirring in argon atmosphere for 300 min while the reaction was monitored by GLPC.

Reaction of 1 with 1,4-Diazabicyclo[2.2.2]octane (DABCO). 461.5 mg (2.80 mmol) of **1** was added into a solution of 272.9 mg (2.40 mmol) of DABCO in 12 ml of acetonitrile in argon atmosphere. The mixture was allowed to stand in argon atmosphere at room temperature, while the reaction was monitored by TLC and GLPC. After 5 h, solvent were distilled off under reduced pressure, the remaining white crystals were washed with hexane and collected, then 1-(4-methylbenzyl)-1,4-diazoniabicyclo[2.2.2]octane thiocyanate was obtained in 99% yield: mp 167.9—169.0 °C; IR (KBr) 2040, 1470, 1380, 1060, 990, 850, 820, and 595 cm^{-1}; NMR ($CDCl_3$) δ=2.41 (3H, s, CH_3–), 3.30 (6H, t, J=6 Hz, $DABCO^+$–), 3.68 (6H, t, J=6 Hz, $DABCO^+$–), 4.77

(2H, s, $-CH_2-$), 7.24 (2H, d, $J=8$ Hz, $-C_6H_4-$), and 7.47 (2H, d, $J=8$ Hz, $-C_6H_4-$).

Found: C, 65.35; H, 7.71; N, 15.04%. Calcd for $C_{15}H_{21}N_3S$: C, 65.42; H, 7.69; N, 15.26%.

Reaction of **1** *with Piperidine.* 338.7 mg (2.08 mmol) of **1** was added into a mixture of 416.2 mg (4.89 mmol) of piperidine and 12 ml of acetonitrile. The reaction mixture was allowed to stand in argon atmosphere at room temperature while the reaction was monitored by TLC and GLPC. After 28 h, the reaction mixture was diluted with 30 ml of water, extracted three times with 10 ml aliquots of ether and the extracts were conbined and washed with 10 ml of water. The solution was dried over anhydrous magnesium sulfate and solvent was evaporated. A colorless oil, obtained, was dissolved in dichloromethane and passed through column of 15 g of Wako activated alumina (200 mesh). The first fraction eluted by dichloromethane gave 30 mg (5%) of **4** which was identified as **4** by comparison with IR and NMR spectra and retention time of GLPC of the authentic sample. Then, the column was washed with ethyl acetate to give 323.2 mg of colorless oil of 1-(4-methylbenzyl)piperidine in 82% yield: IR (neat) 1520, 1440, 1370, 1340, 1300, 1155, 1120, 1100, 1040, 1000, 810, 780, and 490 cm^{-1}; NMR (CCl_4) $\delta=1.25$—1.80 (6H, m, piperidine), 2.04—2.58 (4H, m, piperdine), 2.37 (3H, s, CH_3-), 3.39 (2H, s, $-CH_2-$), 7.01 (2H, d, $J=9$ Hz, $-C_6H_4-$), and 7.12 (2H, d, $J=9$ Hz, $-C_6H_4-$). Colorless crystals of piperidinium thiocyanate 227.9 mg (76%) were obtained from the aqueous layer after evaporation of water and recrystallization of the residue from ethyl acetate: mp 96.5—97.7 °C; IR (KBr) 2960, 2820, 2030, 1435, 1320, 940, and 560 cm^{-1}; NMR (CD_3OD) $\delta=1.50$—2.21 (6H, m, piperidine), 3.06—3.40 (4H, m, piperidine), 4.75 (2H, s, $=N^+H_2$).

Found: C, 49.81; H, 8.39; N, 19.18; S, 21.59%. Calcd for $C_6H_{12}N_2S$; C, 49.96; H, 8.39; N, 19.42; S, 22.23%.

Reaction of **1** *with Diethylamine.* 223.2 mg (1.37 mmol) of **1** was added into a solution of diethylamine 169.1 mg (2.31 mmol) in 7 ml of acetonitrile. The mixture was allowed to stand in argon atmosphere for 15 d at room temperature, while the reaction was monitored by TLC and GLPC. The reaction mixture was diluted with 10 ml of 1% potassium hydroxide aqueous solution, extracted three times each with 10 ml of ether. The combined ether extracts was washed with 10 ml of water, dried over anhydrous magnesium sulfate and upon evaporation of solvent left light yellow oil of *N,N*-diethyl-4-methylbenzylamine (92% yield): IR (neat) 1580, 1515, 1380, 1205, 1170, 820, 800, 755, and 480 cm^{-1}; NMR ($CDCl_3$) $\delta=1.08$ (6H, t, $J=7$ Hz, CH_3CH_2-), 2.37 (3H, s, CH_3-), 2.57 (4H, q, $J=7$ Hz, CH_3CH_2-), 3.56 (2H, s, $-CH_2-$), 7.10 (2H, d, $J=8$ Hz, $-C_6H_4-$), and 7.23 (2H, d, $J=8$ Hz, $-C_6H_4-$).

Reaction of **1** *with Sodium Azide.* 175.7 mg (1.77 mmol) of **1** was added into a mixture of 137.6 mg (2.12 mmol) of sodium azide (containing 10 wt% of methanol and water as stabilizer) suspended in 5 ml of acetonitrile containing 531.3 mg (2.01 mmol) of 18-crown-6 as the phase transfer catalyst. The mixture was refluxed under stirring in argon atmosphere for 20 min, while the reaction was monitored by GLPC. The reaction mixture was diluted with 20 ml of water and extracted three times each with 10 ml of chloroform. Evaporation of the solvent gave a colorless oil of 4-methylbenzyl azide, which was purified through a silica-gel column with 3:1 benzene–hexane: 95% yield; IR (neat) 2080, 1500, 1340, 1250, 800, 750, 530, and 460 cm^{-1}; NMR ($CDCl_3$) $\delta=2.29$ (3H, s, CH_3-), 4.15 (2H, s, $-CH_2-$), and 7.02 (4H, s, $-C_6H_4-$).

Kinetics. A typical run is as follows. To a solution containing the substrate, a solution of DABCO was added at once; the kinetic conditions are shown in Table 5. The temperature was kept at 28 ± 0.05 °C all through the experiment. The conductance of the salt produced in the reaction was measured and recorded automatically, while the concentration of the solution was maintained at constant by comparing with the calibration curve. The rate constants were calculated from the second order rate equation, since the reaction of halides with amine has been known as the Menschutkin reaction which obeyed the second-order rate equation.

Molecular Orbital Calculation. The molecular and electronic structures of benzyl thiocyanate and various nucleophiles were calculated by means of the closed-shell SCF INDO method.[11] All the molecular structures were optimized except the phenyl group in benzyl thiocyanate and benzenethiolate anion. In the calculation of the orbital interaction energies, the resonance integrals were approximated to be proportional to the overlap integrals; $S_{rs}\beta_0$, where S_{rs} is the overal integral between atomic orbitals r and s, and β_0 is a constant. For the donor orbitals, only the HOMO LCAO coefficients on the nucleophilic atom were taken into account. Thus the values listed in Table 3 are:

$$\sum_{m}^{unocc} \frac{(\sum_{r} C_{rm}C_{s,HOMO}S_{rs})^2}{\varepsilon_{HOMO}-\varepsilon_m},$$

where S_{rs} was evaluated between the r AO of benzyl thiocyanate and the s-type AO of the nucleophilic atom in each nucleophile which is placed at 2.0 Å distance along the direction cited in Fig. 5.

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