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AM1 Calculations for Regioselectivities and Reactivities Observed in Cyanation of 3-Substituted Pyrazine 1-Oxides with Trimethylsilyl Cyanide

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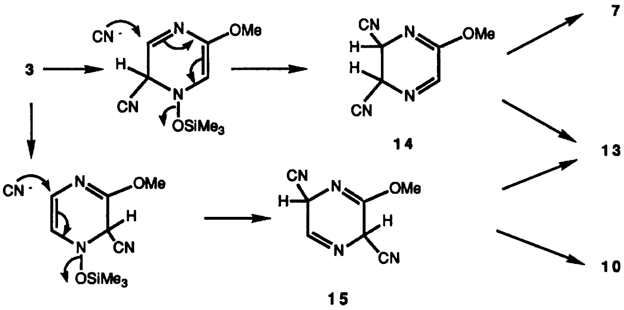
Regioselectivities and reactivities previously reported in the reactions of 3-amino-, 3-cyano-, 3-mehoxy-, and 3-methoxycarbonylpyrazine 1-oxide with trimethylsilyl cyanide were corroborated on the basis of semiempirical molecular orbital calculations (AM method) involving an approach of a cyanide ion to the reactive sites.

Recently, two of the authors of this paper reported the cyanation of 3-substituted pyrazine 1-oxides with trimethylsilyl cyanide to yield, with a loss of the *N*-oxide oxygen, the corresponding cyanopyrazines.[1] The substituent on the *N*-oxide was found to affect remarkably both the reactivity and the regioselectivity of the cyanation.[1] For instance, 3-cyanopyrazine 1-oxide (**1**) underwent cyanation even at room temperature to produce 2,5-dicyanopyrazine (**6**) in a 24% yield[2] after being stirred in acetonitrile for 6 h. Similar reaction of 3-aminopyrazine 1-oxide (**2**) required more forced conditions to afford 2-amino-3-cyanopyrazine (**9**) in a 93% yield by treatment in refluxing acetonitrile for 6 h. Under the same conditions, however, 3-methoxypyrazine 1-oxide (**3**) formed an isomeric mixture of 2-cyano-3-methoxypyrazine (**10**) (43%) and 2-cyano-6-methoxypyrazine (**13**) (19%), together with a 16% recovery of the unreacted 1-oxide **3**. A similar situation was observed in the cyanation of 3-methoxycarbonylpyrazine 1-oxide (**4**), which gave a mixture of 2-cyano-5-methoxycarbonylpyrazine (**8**) (32%) and 2-cyano-3-methoxycarbonylpyrazine (**11**) (28%) by the same conditions except the reaction time was prolonged to 18 h. At that time, the starting material **4** still remained as judged from TLC, but could not be isolated. In the case of 3-chloropyrazine 1-oxide **5**, the reaction did not occur even under the most severe conditions, but did in the presence of such a Lewis acid such as zinc bromide to afford 2-chloro-3-cyanopyrazine **12** in a 76% yield (Chart 1).

Thus, the reactivity decreased according to the sequence CN > NH_2 > OMe > COOMe > Cl. In terms of regioselectivity, 2-cyano-6-methoxypyrazine (**13**) in the above products was the only exception, because it resulted from substitution at the β-position of the *N*-oxide function. One possible mechanism for competitive formation of **10** and **13** is shown in Scheme 1, in which two possible intermediates, **14** and **15**, are involved. The former, however, may be ruled out because we detecting no 2-cyano-5-methoxypyrazine (**7**) which must be yielded from **14**, if the elimination of hydrogen cyanide is not highly regioselective. Thus, a cyanide ion attacked the C-2 position of 3-amino-, 3-methoxy-, and 3-chloropyrazine 1-oxide with high selectivity, whereas the regioselectivity was almost lost in the 3-methoxycarbonyl derivative.



Scheme 1.

In this paper, we provide an explanation for the regioselectivities and reactivities of the cyanation on the basis of semiempirical molecular orbital calculations.

Results and Discussion

The AM1 method was employed instead of the PM3 method,[3] because in contrast with the case calculated by the former method, the plane of the methoxycarbonyl group calculated by the latter method was almost orthogonal to that of the pyrazine ring in 3-methoxycarbonylpyrazine 1-oxide (**4**), in conflict with the IR data (an α,β-unsaturated ester absorption band appeared at 1720 cm^{-1}). To obtain the most stable isomer of the 3-substituent in **3** and **4**, the calculations were performed for each pair of "*cis*" and "*trans*" models illustrated in Fig. 1 and the results are shown in Table 1. In **3**, the "*cis*" isomer was much more stable than the "*trans*" isomer, suggesting that the electrostatic repulsion between the lone pair electrons on N-4 and that on O-8 (methoxyl group) is stronger than the steric repulsion between the lone pair electrons on N-4 and the methyl group.[4] In the case of **4**, the heats of formation of both isomers are almost the same, but the methoxycarbonyl group occupies almost the same plane as the pyrazine ring in the "*cis*" isomer, whereas it deviates about 40° in the "*trans*" isomer. The latter may be caused by a balance of unfavorable electrostatic repulsion between the lone pair electrons on N-4 and those of the carbonyl oxygen atom and favorable conjugation between the carbonyl group and the ring.

We assumed the following two reaction paths; a cyanide ion attacks the pyrazine ring before[5] or after silylation at the oxygen atom (Scheme 2). In the former

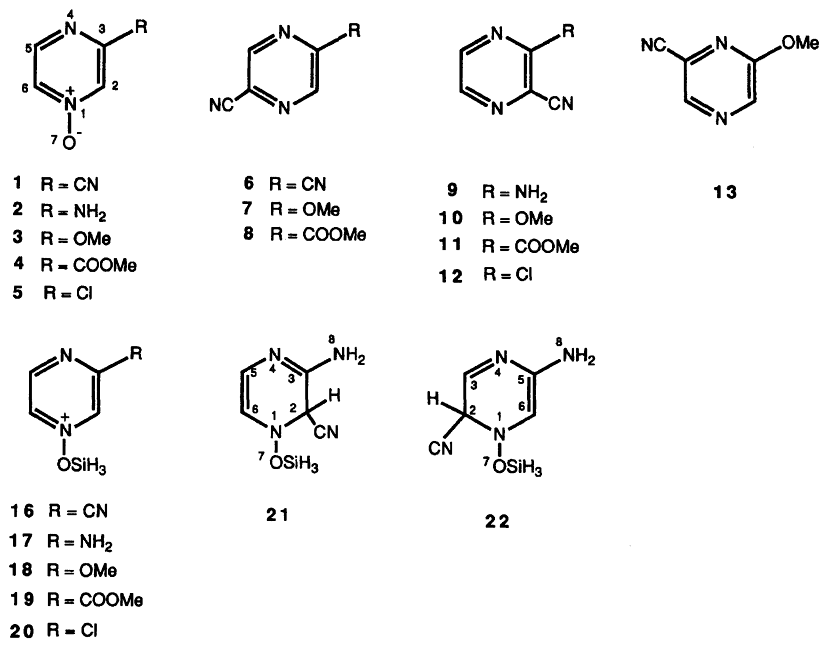
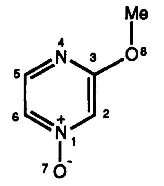
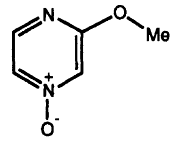


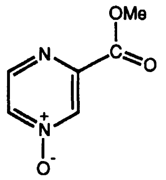
Chart 1. Chemical formula.



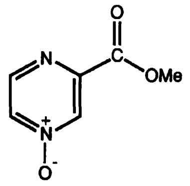
3 (*cis*)



3 (*trans*)



4 (*cis*)



4 (*trans*)

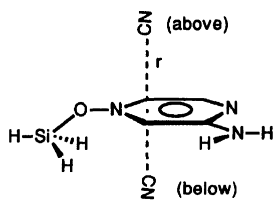


Fig. 1. Above and below approaches are illustrated in the case of silylated 3-substituted 3-aminopyrazine 1-oxide.

Table 1. Heats of Formation of 3-Substituted Pyrazine 1-Oxides, Energy Levels and Coefficients at C-2 and C-6 of LUMO and Net Charges at C-2 and C-6 Calculated by AM1

Compound	Heats of formation	Energy levels	Coefficients		Net atomic charges	
	kJ mol^{-1}	eV	C-2	C-6	C-2	C-6
1	372.6	−1.497	0.391	−0.500	−0.219	−0.241
2	210.6	−0.370	0.465	−0.379	−0.332	−0.306
3 (*trans*)	74.1	−0.634	0.506	−0.317	−0.330	−0.289
3 (*cis*)	55.3	−0.569	0.502	−0.357	−0.278	−0.287
4 (*trans*)	−107.2	−1.299	0.550	−0.507	−0.203	−0.237
4 (*cis*)	−106.3	−1.400	0.387	−0.500	−0.201	−0.234
5	193.4	−1.020	0.418	−0.503	−0.250	−0.256

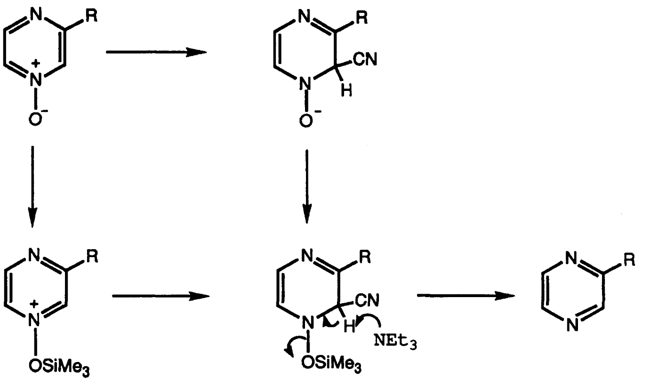
mechanism, the *N*-oxides having lower LUMO energy levels should be better electrophiles and react more readily. The LUMO energy levels calculated decreased according to the sequence NH_2 > OMe > Cl >COOMe

Table 2. Energy Levels and Coefficients at O-7, C-2, and C-6 of HOMO of 3-Substituted Pyrazine 1-Oxides and Net Atomic Charges at O-7

Compound	Energy levels	Coefficients			Net atomic charges
	eV	C-2	C-6	O-7	O-7
1	−10.107	0.408	0.448	−0.653	−0.390
2	−9.400	−0.068	0.623	−0.423	−0.409
3 (*trans*)	−9.694	0.271	0.535	−0.612	−0.401
3 (*cis*)	−9.679	0.386	0.467	−0.645	−0.399
4 (*trans*)	−9.946	0.421	0.433	−0.656	−0.396
4 (*cis*)	−9.930	0.425	0.429	−0.658	−0.402
5	−9.909	0.402	0.453	−0.649	−0.394

Table 3. Energy Levels, Coefficients, and Net Atomic Charges at C-2 and C-3 of LUMO of Silylated 3-Substituted Pyrazine 1-Oxides Calculated by AM1

Compound	Heats of formation	Energy levels	Coefficients		Net atomic charges	
	kJ mol^{-1}	eV	C-2	C-6	C-2	C-6
16	1035.2	−6.393	0.337	0.522	−0.057	−0.063
17	822.1	−5.577	0.463	0.427	−0.207	−0.165
18 (*trans*)	708.3	−5.889	0.450	0.447	−0.189	−0.120
18 (*cis*)	681.1	−5.822	0.487	0.401	−0.119	−0.135
19 (*trans*)	540.0	−6.184	0.346	0.520	−0.033	−0.059
19 (*cis*)	538.3	−6.173	0.346	0.518	−0.038	−0.059
20	841.0	−6.158	0.415	0.473	−0.087	−0.084



Scheme 2.

> CN, and did not agree with the reactivities observed (Table 1). Two cases must be considered in the latter mechanism, that is, the rate-determining step is the silylation at the oxygen atom (O-7) or the attack of a cyanide ion to a silylated pyrazine. In the former, the *N*-oxides having higher HOMO energy levels should be more reactive, disagreeing with the experimental results (Table 2). On the other hand, in the latter, the *O*-silyl derivatives having lower LUMO energy levels should be more reactive. Siloxy derivatives used as model compounds of the trimethylsilyloxy derivatives were calculated, but the results again disagreed with the observed reactivities (Table 3). Although regioselectivities in both cases should be controlled by the coefficients and/or net charges at C-2 and C-6 of the LUMO, they were not reproducible. Thus, the energy levels of HOMO and LUMO as well as their coefficients and charges at C-2 and C-6 seem not to give a rationale for the present experimental results, if these cyanations occur by the same mechanism.

We next turned our attention to a different standpoint for elucidation of the cyanation, that is, by approach of a cyanide ion to the active sites of 3-substituted pyrazine 1-oxide and the 1-siloxy derivatives. However, in the fully-optimized structure of **17**, the silyl group is close to the C-6 position. If this structure is employed as input data, the approach of a cyanide ion at C-6 should be unfavorable on steric grounds. Therefore, the dihedral angle (Si–O–N–C-2) of **17** was fixed at 90° first and the others were fullly optimized. The geometry thus obtained was used for the calculation with a cyanide ion at 2.0 Å (Fig. 1). During the calculation, the dihedral angle was also optimized. Similar treatments were performed for other silylated 3-substituted pyrazine 1-oxides. The distance between the nucleophile and the ring carbon was varied from 2.0 to 1.5 Å, and the heats of formation were obtained for selected points in this space. The geometry obtained at 1.5 Å was used as input data for complete optimization including the distance. These results are summarized in Tables 4 and 5 for a favorable approach to the C-2 and C-6 carbons, and parts of them are illustrated in Figs. 2 and 3. In the cases of **1**, **4**, and **17**, heats of formation for the cyanide ion approaching the target carbon were in almost the same calculated range as those from the other side, and only one energy profile in each case is shown in the Figs. It was noteworthy that the "*trans*" isomer (geometrical definition is the same as that shown in Fig. 1) of silyl-

Table 4. Heats of Formation[a)] Calculated by the AM1 Method as a Function of Approach of a Cyanide Ion to 3-Substituted Pyrazine 1-Oxide[b,c)]

Distance	**1**			**2**			**3** (*cis*)			**4** (*trans*)		
r/Å	C-2	C-6	ΔH[d)]	C-2	C-6	ΔH	C-2	C-6	ΔH	C-2	C-6	ΔH
2.0	437.9	434.5	3.4	332.4	339.5	−7.1				−39.8	−42.7	2.9
1.9	414.4	410.2	4.2	317.3	321.1	−3.8	162.0	162.0	0.0	−64.5	−68.7	4.2
1.8	383.0	377.6	5.4	292.6	293.9	−1.3				−96.7	−102.6	5.9
1.7	345.8	339.1	6.7	260.0	259.5	−0.5	102.6	100.9	1.7	−134.8	−142.3	7.5
1.6	310.2	301.4	8.8	226.9	225.6	1.3				−171.2	−180.8	9.6
1.5	288.4	278.4	10.0	206.8	205.1	1.7	49.0	46.5	2.5	−193.4	−204.7	11.3
Opt	287.2	276.7	10.5	205.5	203.9	1.6	48.1	45.2	2.9	−194.6	−206.4	11.8

a) kJ mol^{-1}. b) A cyanide ion put on just above or below[6)] the 2- and 6-positions of 3-substituted pyrazine 1-oxide and its distance (r) made a reaction coordinate and others were fully optimized. c) The more stable approach only was described. d) Energy differences of these two pathways; calculated by heat of formation for approach to C-2 minus that of C-6.

Table 5. Heats of Formation[a)] Calculated by the AM1 Method as a Function of Approach of a Cyanide Ion to Silylated 3-Substituted Pyrazine 1-Oxide[b,c)]

Distance	**16**			**17**			**18** (*cis*)			**19** (*trans*)		
r/Å	C-2	C-6	ΔH[d)]	C-2	C-6	ΔH	C-2	C-6	ΔH	C-2	C-6	ΔH
2.0				474.3	491.0	−16.7	324.0	334.5	−10.5			
1.9	602.8	589.8	13.0	437.0	452.1	−15.1	283.8	295.5	−11.7	124.7	110.9	13.8
1.8				392.6	406.9	−14.3	237.8	250.3	−12.5			
1.7	508.6	495.2	13.4	345.3	357.9	−12.6	188.4	202.2	−13.8	30.6	15.1	15.5
1.6				301.4	313.5	−12.1	143.2	157.8	−14.6			
1.5	436.6	422.8	13.8	274.2	285.5	−11.3	115.1	129.8	−14.7	−42.3	−59.0	16.7
Opt	433.7	419.9	13.8	271.7	282.6	−10.9	112.2	127.3	−15.1	−45.2	−62.0	16.8

a) kJ mol^{-1}. b) A cyanide ion put on just above or below[6)] the 2- and 6-positions of silylated 3-substituted pyrazine 1-oxide and its distance (r) made a reaction coordinate and others were fully optimized. c) The more stable approach only was described. d) Energy differences of these two pathways; calculated by heat of formation for approach to C-2 minus that of C-6.

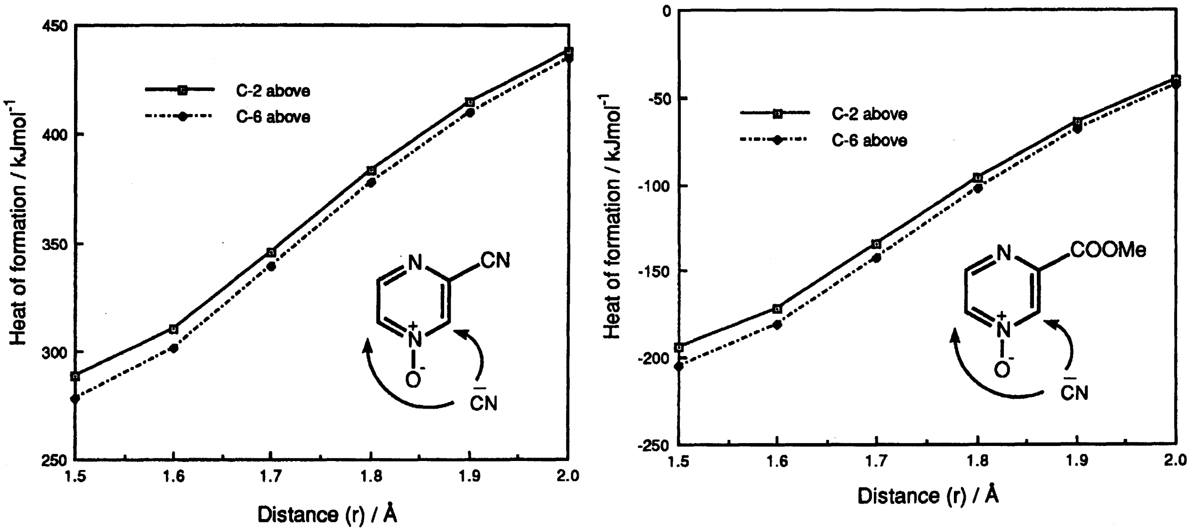


Fig. 2. Heats of formation vs. reaction coordinates (r) calculated by the AM1 method in the approach of a cyanide ion to C-2 and C-6 of **1** and **4** {above, see Ref. 6}.

ated 3-methoxypyrazine 1-oxide (**18**) isomerized to the "*cis*" isomer during the optimization taking the cyanide ion at 2.0 Å from the marked carbons. Approach from below[6)] the C-6 carbon was only an example to converge without isomerization, but the structure calculated was less stable than the "*cis*" structure calculated independently by 16.7 kJ mol^{-1}.

Apparently, exclusive attack of a cyanide ion at the

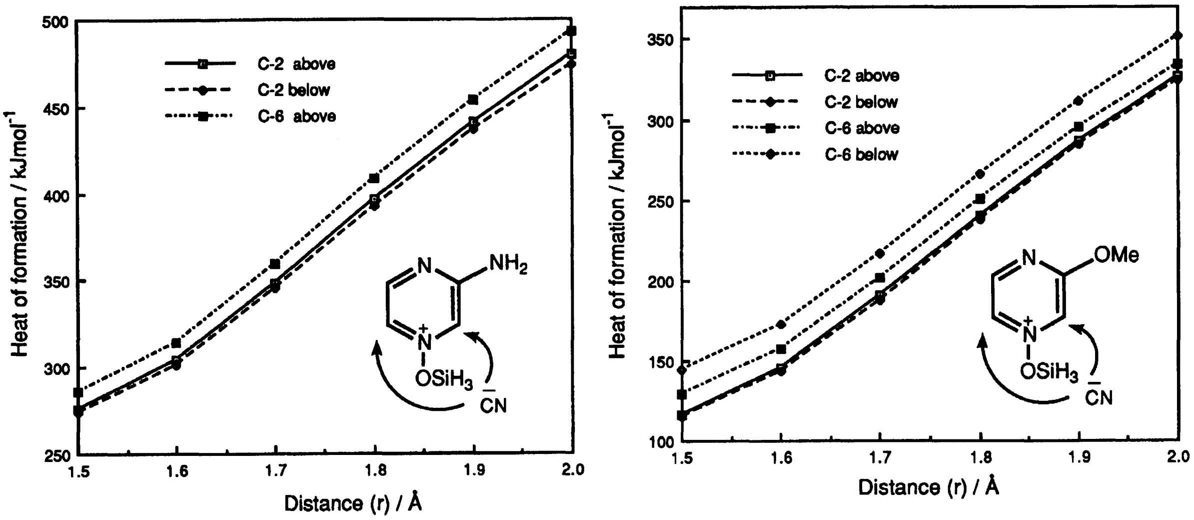


Fig. 3. Heats of formation vs. reaction coordinates (*r*) calculated by the AM1 method in the approach of a cyanide ion to C-2 and C-6 of **17** and **18** {above and below, see Ref. 6}.

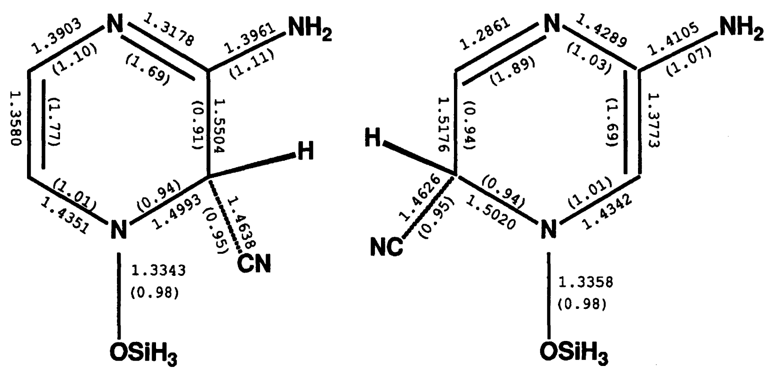
C-2 position of 3-amino **2** and 3-methoxy derivatives **3** could not be reproduced by unsilylated derivatives, but only by silyl ones. The average energy difference from 1.5 to 2.0 Å reached 13.7 and 13.0 kJ mol^{-1} in the cases of **17** and **18**, respectively. Conversely, the regioselectivity observed in 3-methoxycarbonylpyrazine 1-oxide is reproducible by the direct attack of the ion to the carbon atom on the 1-oxide derivatives **4**. The alternative route is, however, ruled out, because the regioselectivity calculated by the use of **19** was too high (Table 5). These conclusions, not conflicting with the energy levels of HOMO and LUMO (Tables 1, 2, and 3), were acceptable, since the electron-withdrawing methoxycarbonyl group activates a nucleophilic attack to the pyrazine ring, but deactivates an electrophilic silylation at the oxygen atom. On the other hand, the electron-donating amino and methoxyl groups have the opposite effects.

The higher reactivity of 3-amino derivative **2** than that of 3-methoxy derivative **3** may be explained if silylation is the rate-determining step, followed by a facile attack of a cyanide ion. Such a speculation agrees with HOMO of **2** and **3** and with higher electron donation of the amino group than the methoxyl group.

The chlorine atom of 3-chloropyrazine 1-oxide (**5**) should not be enough to activate an attack of a cyanide ion at the pyrazine ring itself or to promote silylation. Thus, the chloro derivative reacted after activation with a Lewis acid such as zinc bromide, in which the same regioselectivity should be observed as that of silylated derivatives of **2** and **3**, because the chloro group is also categorized as an *o*, *p*-director just as amino and methoxyl groups are.

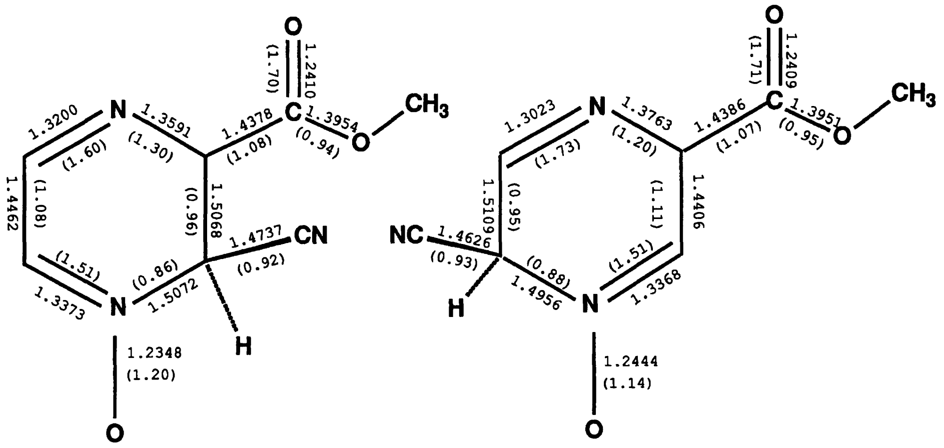
Why does a cyanide ion attack the C-2 position of 2-amino- and 2-methoxy-4-siloxypyrazines with high regioselectivity and why does it attack the C-2 and C-6 positions of 3-methoxycarbonylpyrazine 1-oxide with almost equal proportion? To answer these questions the structures of complexes obtained by full optimization (involving the reaction coordinate) were compared. For example, bond lengths as well as bond orders and valencies of **21** and **22**, which are conceivable as the intermediates of 1-oxide **2**, are depicted in Fig. 4. In intermediary **21**, an electron-withdrawing carbon–nitrogen double bond (C-3–N-4) is stabilized by conjugation with the amino group at C-3. Such a conjugation should be more favorable than the enamine-like conjugation observed in **22**. In fact, the bond length and bond order and valency of C-3–N-8 of **21** were shorter by 0.0144 Å and higher by 0.04 than the corresponding values of **22**. This surmise gives a rationale, at least partly, as to why **21** is more stable than the alternative isomer **22** as calculated. A similar argument is applicable to the case of 3-methoxy derivative **18**. In compounds **23** and **24**, the present level of calculation suggests that the canonical structures **23a** and **24a** are more important than the alternative **23** and **24**, respectively, as judged from the bond lengths, bond order and valencies, and charges (Fig. 5), and it also revealed that all ring atoms occupy almost the same plane in **24**, whereas only the C-3 position of **23** slightly deviates from the plane (Scheme 3). Therefore, the former should be slightly more stable than the latter, as indicated by the calculation. A similar geometrical difference was observed in the case of 3-cyano derivative **1**, giving a rationale for the predominant attack at C-6.

In conclusion, the reactivities and regioselectivities of 3-substituted pyrazine 1-oxides with trimethylsilyl cyanide are explainable on the basis of the assumption derived, by the present level calculation, that cyanation occurs directly in the cases of 3-cyano- and 3-methoxycarbonylpyrazine 1-oxide, whereas it occurs after the



21 **22**

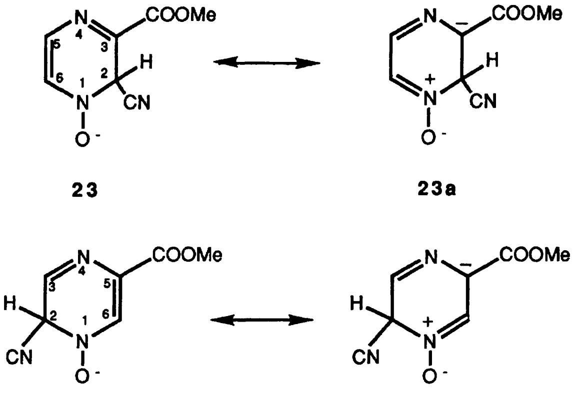
Fig. 4. Bond lengths, bond orders, and valencies (parentheses) of fully optimized structures of **21** and **22**.



23 **24**

Net atomic charge at C-3; -0.39 Net atomic charge at C-5; -0.36

Fig. 5. Bond lengths, bond orders, and valencies (parentheses), and net atomic charges at C-3 of **23** and C-5 of **24**.



Scheme 3.

rate-determining silylation in the cases of 3-amino- and 3-methoxypyrazine 1-oxides.

Molecular orbital calculations were performed with a FACOM M-360AP computer at the Education Center for Information Processing of Yokohama City University, and we thank its staff for their kind help with the calculations.

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2) The low yield was the results of instability of the product under the reaction conditions because the cyanation reaction in refluxing acetonitrile for 6 h caused degradation and no product was given.

3) "MOPAC Ver. 5," J. J. Stewart, *QCPE Bull.* **9**, 10 (1989); Revised as Ver. 5.01 by Tsuneo Hirano, University of Tokyo, for the HITAC machine, *JCPE Newsletter*, **1**, 10 (1989).

4) The present calculation does not involve solvents, therefore, it is likely that the electrostatic repulsion may be overestimated.

5) It is well-known that a pyrazine is less reactive towards electrophiles than benzene and pyridine.

6) Approach from below and above indicates that a cyanide ion attacks from below or above the pyrazine plane, in which the substituent at C-3 goes on the right side and the silyl group is below the plane as illustrated in the Fig. 1.