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Regioselectivity in the Amination of Azines: Reaction of Pyrazine Derivatives with *O*-Mesitylenesulfonylhydroxylamine*

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Abstract—Treatment of 2-X-substituted pyrazines [X = H, Me, Et, Pr, *i*-Pr, *t*-Bu, MeCH(OH), H_2N, AcNH] with *O*-mesitylenesulfonylhydroxylamine gave the corresponding 2-X- and 3-X-(1-amino)pyrazin-1-ium mesitylenesulfonates. 2-Alkylpyrazines (X = Me, Et, Pr, *i*-Pr) displayed a correlation between the logarithms of the concentration ratio of 2- and 3-substituted cations and substituent steric constants. Wider series of substituted pyrazines [X = H, Me, Et, Pr, *i*-Pr, MeCH(OH), H_2N, AcNH] conformed to a multiparameter correlation between the logarithms of the concentration ratio of 2- and 3-substituted cations, on the one hand, and substituent constants σ_I, σ_R^o, and E_s^o, on the other. The obtained data on the regioselectivity of amination of pyrazines were interpreted in terms of DFT/PBE/3Z quantum-chemical calculations.

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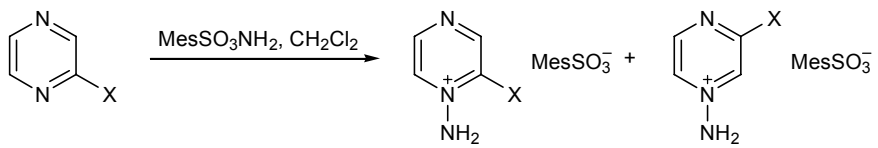
Salts derived from N-amino-substituted nitrogen-containing heterocycles are widely used as reagents for the amination of arenes [3] and for the preparation of imines [4] and various heterocyclic and other compounds [5–17]. Such salts having several nitrogen atoms in the ring are also promising as energetic materials [18–20]. Salts of *N*-amino cations are usually prepared by direct amination of nitrogen-containing heterocycles with various aminating agents; among the latter, *O*-mesitylenesulfonylhydroxylamine (MSH) is used most widely [11–13].

If a heteroaromatic compounds contains nitrogen atoms with different environments, amination regioselectivity problem arises [13, 21]. We previously studied reactions of 3-bromo-, 4-methyl-, and 5-nitro-1,10-phenanthrolines with MSH and found that the ratio of the resulting isomeric amino cations is determined by their relative stability [21]. The goal of the present work was to reveal factors responsible for regioselectivity in the amination of pyrazine derivatives. The latter were selected as substrates, taking into account that pyrazines are widely used in the synthesis of N-amino derivatives [13]. In addition, unlike 1,10-phenanthroline derivatives listed above, the substituent in 2-X-pyrazines is contiguous to the reaction center, and the nitrogen atoms are present in a single ring, which could endow the amination process with some specificity.

The reaction of 2-substituted pyrazines **Ia**–**Ii** with MSH in methylene chloride resulted in the formation

Scheme 1.

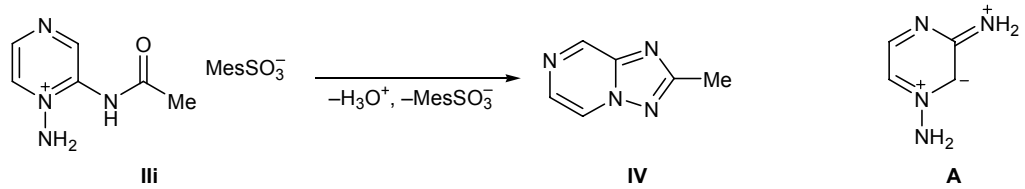


Ia–Ij **IIa–IIe, IIg–IIi** **IIIa–IIIi**

X = H (**a**), Me (**b**), Et (**c**), Pr (**d**), *i*-Pr (**e**), *t*-Bu (**f**), MeCH(OH) (**g**), H_2N (**h**), AcNH (**i**), CN (**j**).

* For preliminary communications, see [1, 2].

Scheme 2.



IIi IV A

Table 1. [1]H NMR spectra of *N*-aminopyrazinium salts **II** and **III** in DMSO-d_6 at 25°C

Cation no.	Chemical shifts δ,[a] ppm (*J*, Hz)					
	X	2-H	3-H	5-H	6-H	NH_2[b]
IIa	–	8.74 d.d.d (*J* = 4.0, 1.6, 1.0)	9.14 d.d (*J* = 4.0, 1.0)	9.14 d.d (*J* = 4.0, 1.0)	8.74 d.d.d (*J* = 4.0, 1.6, 1.0)	9.60
IIb	2.67 d.d.d (3H, *J* = 0.8, 0.8, 0.4)	–	9.13 q.d (*J* = 0.8, 0.7)	8.97 d.q (*J* = 4.0, 0.8)	8.80 d.d.q (*J* = 4.0, 0.7, 0.4)	9.08
IIIb	2.60 d.d.d (3H, *J* = 0.7, 0.7, 0.7)	8.71 d.q.d (*J* = 1.5, 0.7, 0.7)	–	9.01 d.q.d (*J* = 3.9, 0.7, 0.7)	8.62 d.d.q (*J* = 3.9, 1.5, 0.7)	9.51
IIc	1.30 t (3H, *J* = 7.4), 3.05 q.d.d.d (2H, *J* = 7.4, 0.8, 0.7, 0.4)	–	9.08 t.d (*J* = 0.8, 0.8)	8.98 d.t (*J* = 4.0, 0.7)	8.84 d.d.t (*J* = 4.0, 0.8, 0.4)	9.6
IIIc	1.24 t (3H, *J* = 7.6), 2.87 q.d.d (2H, *J* = 7.6, 0.6, 0.5)	8.78 d.d.t (*J* = 1.6, 0.9, 0.5)	–	9.03 d.d (*J* = 3.9, 0.9)	8.66 d.d.t (*J* = 3.9, 1.6, 0.6)	9.6
IId	0.95 t (3H, *J* = 7.4), 1.71 t.q (2H, *J* = 7.8, 7.4), 3.01 t (2H, *J* = 7.8)	–	9.08 d (*J* = 0.8)	8.98 d (*J* = 4.0)	8.85 d.d (*J* = 4.0, 0.8)	9.6
IIId	0.88 t (3H, *J* = 7.4), 1.66 t.q (2H, *J* = 7.6, 7.4), 2.80 t (2H, *J* = 7.6)	8.80 d.d (*J* = 1.6, 0.9)	–	9.04 d.d (*J* = 3.9, 0.9)	8.68 d.d (*J* = 3.9, 1.6)	9.1
IIe[c]	1.32 d (6H, *J* = 6.8), 3.64 sept (1H, *J* = 6.8)	–	9.19	8.99 d (*J* = 4.0)	8.81 d (*J* = 4.0)	9.5
IIIe	1.23 d (6H, *J* = 6.9), 3.16 sept (1H, *J* = 6.9)	8.83 d.d (*J* = 1.5, 0.9)	–	9.05 d.d (*J* = 3.9, 0.9)	8.67 d.d (*J* = 3.9, 1.5)	9.5
IIIf	1.35 s (9H)	8.82 d.d (*J* = 1.5, 0.9)	–	9.10 d.d (*J* = 3.8, 0.9)	8.63 d.d (*J* = 3.8, 1.5)	9.5
IIg	1.55 d (3H, *J* = 6.6), 5.34 q.d.d (1H, *J* = 6.6, 0.6, 0.6), 5.2 br.s (1H)	–	9.22 d.d (*J* = 0.8, 0.6)	9.05 d.d (*J* = 4.0, 0.6)	8.81 d.d (*J* = 4.0, 0.8)	9.1
IIIg	1.44 d (3H, *J* = 6.6), 4.91 q.d.d (1H, *J* = 6.6, 0.8, 0.8), 5.2 br.s (1H)	8.80 d.d.d (*J* = 1.7, 0.9, 0.8)	–	9.04 d.d (*J* = 3.9, 0.9)	8.66 d.d.d (*J* = 3.9, 1.7, 0.8)	9.6
IIh	8.84 br.s (2H)	–	8.61 d (*J* = 1.0)	7.90 d (*J* = 4.4)	8.07 d.d (*J* = 4.4, 1.0)	7.14
IIIh	7.68 br.s (2H)	7.84 d.d (*J* = 1.5, 0.9)	–	7.80 d.d (*J* = 3.8, 1.5)	8.37 d.d (*J* = 3.8, 0.9)	9.0
IIIi	2.20 s (3H), 11.6 br.s (1H)	9.42 d.d (*J* = 1.5, 0.9)	–	8.83 d.d (*J* = 3.9, 0.9)	8.43 d.d (*J* = 3.9, 1.5)	9.6

[a] The chemical shifts were measured relative to the residual solvent signal (DMSO, δ 2.50 ppm).
[b] Broadened singlet (2H).
[c] Some coupling constants were not determined because of low signal intensity.

Table 2. ^{13}C NMR spectra of *N*-aminopyrazinium salts **II** and **III** in DMSO-d_6 at 25°C

Cation no.	Chemical shifts δ_C,[a] ppm (J_{CH}, Hz)				
	substituent X	C^2	C^3	C^5	C^6
IIa	–	127.8 (197.3)	150.0 (195.2)	150.0 (195.2)	127.8 (197.3)
IIb	15.4 (131.9)	140.2	151.0 (194.0)	146.6 (195.0)	128.2 (196.5)
IIIb	21.8 (129.6)	126.9 (198.8)	159.7	148.8 (194.0)	125.2 (198.2)
IIc	27.8 (127.7), 13.2 (128.9)	143.7	149.6 (192.7)	146.8 (195.2)	128.5 (196.0)
IIIc	28.5(129.7), 12.1 (127.6)	126.5 (194.6)	164.1	149.1 (194.0)	125.5 (197.6)
IId	13.4 (127.5), 22.0 (127.4), 36.5 (127.5)	142.6	150.3 (193.1)	146.8 (195.4)	128.7[b]
IIId	13.3 (125.6), 21.2 (128.2), 36.9 (129.5)	126.7 (194.7)	163.0	149.1 (194.2)	125.5 (197.9)
IIIe[c]	21.1 (127.7), 33.9 (130.9)	125.7 (194.2)	167.4	149.0 (194.2)	125.5 (197.8)
IIIf	28.6 (127.2), 37.3	125.3 (197.5)	169.4	148.6 (192.5)	124.7 (194.3)
IIg	19.5 (128.9), 62.7 (148.2)	143.9	148.0 (191)	147.6 (191)	128.6 (196.7)
IIIg	22.8 (128.0), 67.5 (145.4)	124.4 (197.0)	166.9	148.6 (194.7)	125.8 (197.7)
IIh		147.1	141.3 (195.8)	130.4 (194.6)	130.6 (193.6)
IIIh		114.0 (202)	165.5	148.3 (194)	116.2 (199)
IIIi	23.8 (129.0), 170.6	118.3 (201.6)	164.1	148.1 (194.5)	123.0 (199.0)

[a] The chemical shifts were measured relative to the solvent signal (DMSO-d_6, δ_C 39.50 ppm).
[b] The coupling constant was not determined due to superposition of other signals.
[c] The data for cation **IIe** are not given because of its low concentration.

of isomeric cations **IIa**–**IIe**, **IIg**, **IIh** and **IIIb**–**IIIi** (Scheme 1). No amination of pyrazine-2-carbonitrile (**Ij**) was observed, whereas in the reaction with 2-*tert*-butylpyrazine (**If**) only one isomeric cation **IIIf** was formed. We failed to identify cation **IIi**, for it underwent intramolecular cyclization to 2-methyl[1,2,4]triazolo[1,5-*a*]pyrazine (**IV**) (Scheme 2).

The structure of *N*-aminopyrazinium salts **II** and **III** was determined by ^1H and ^{13}C NMR spectroscopy (Tables 1, 2), and the structure of **IIa**, **IIh**, and **IIIi** was additionally proved by X-ray analysis [22]. Signals in the NMR spectra were assigned using various correlation techniques, ^1H-2D NOESY and two-dimensional ^1H–^1H and ^1H–^{13}C COSY. NOESY experiments

Table 3. Concentration ratios of isomeric *N*-aminopyrazinium ions **II** and **III**, substituent constants σ_I, E_s, E_s°, σ_R°, and *F*, and calculated energy barriers for the amination process ($E_{calc}^{\neq}$)

X	log([**II**]/[**III**])[a]	σ_I [24]	σ_R° [25, 26]	E_s [25]	E_s° [b]	*F* [27]	$E_{calc}^{\neq}$,[c] kJ/mol	$\Delta E_{calc}^{\neq}$, kJ/mol
H	0.0	0	0.00	1.24	0.25	–0.28	62.8	0.00
Me	–0.173±0.003	–0.01	–0.10	0.00	0.00	0.00	57.3 (57.7)	–0.38
Et	–0.498±0.017	–0.01	–0.10	–0.07	–0.27	0.73	59.3 (58.5)	0.84
Pr	–0.478±0.012	–0.01	–0.11	–0.36	–0.56	0.52	63.3 (58.4)	1.17
i-Pr	–1.020±0.055	0.01	–0.12	–0.47	–0.87	2.12	72.0 (58.6)	13.43
MeCH(OH)	–0.479±0.003	0.04	–0.08	0.09	–0.44	0.64	73.3 (64.2)	9.08
NH_2	0.406±0.015	0.17	–0.47	0.00[d]	0.00	–	36.3 (54.1)	–17.87
AcNH	–0.473±0.019	0.28	–0.41	–0.75[d]	–0.95	–	[e]	[e]

[a] Average values from 5–8 measurements by ^1H NMR.
[b] Calculated by the equation $E_s^\circ = E_s - 0.33(3 - n_H) + 0.13n_C$ [27].
[c] Activation barriers for the amination with formation of 3-substituted isomer are given in parentheses.
[d] Calculated in terms of the isostericity concept [27].
[e] Transition state leading to cation **IIi** was not found.

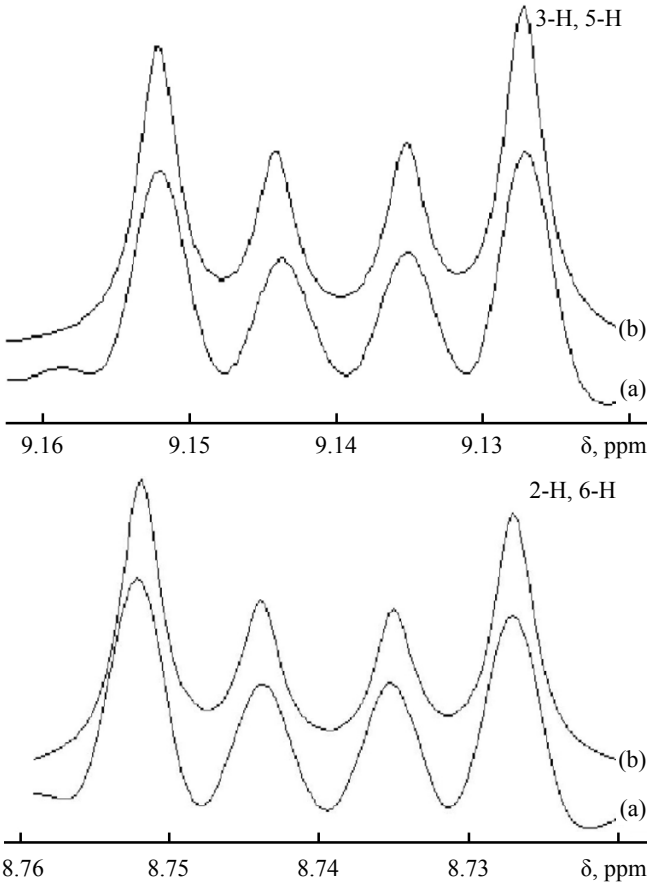


Fig. 1. (a) Experimental and (b) calculated ^{1}H NMR spectra of cation **IIa**.

revealed nuclear Overhauser effects for spatially close protons in the NH_2 group and 2-H (6-H). The 2-H and C^2 signals in the ^{1}H and ^{13}C NMR spectra of cation **IIIh** were observed in a relatively strong field, which

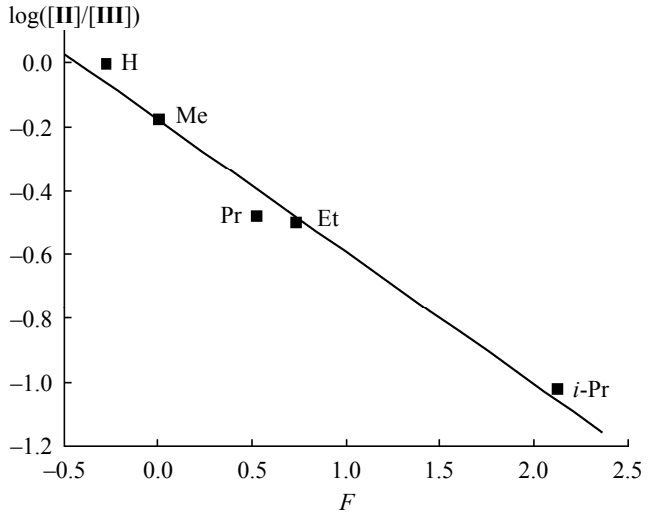


Fig. 2. Plot of log[(**II**)/(**III**)] versus substituent steric constants *F*.

may be due to significant contribution of canonical structure **A**. In most cases, signals from endocyclic carbon atoms remote from the N^+–NH_2 fragment appeared in a weaker field than those neighboring to that fragment. Presumably, this is the result of polarization of the C–C bonds toward electron-withdrawing N^+–NH_2 group. The coupling constants J_{HH} were determined by comparing the calculated and experimental spectra. As an example, Fig. 1 shows the calculated and experimental ^{1}H NMR spectra of cation **IIa** in the aromatic region. Fairly large absolute values of the direct coupling constants $^1J_{CH}$ (191–202 Hz) should be noted. Analogous values of $^1J_{CH}$ were observed previously for *N*-methylpyrazinium [23].

The concentration ratio of isomeric cations **II** and **III** was determined on the basis of the ^{1}H NMR spectra. It strongly depends on the substituent nature (Table 3) and is kinetically controlled. This follows from the fact that the ^{1}H NMR spectra of **IIh** and **IIIi** remained unchanged after heating for 4 h at 100°C in DMSO. Likewise, according to the ^{1}H NMR data, heating of a solution of 1-aminopyrazinium salt in DMSO in the presence of 5 equiv of pyridine or mesitylene did not result in amino group transfer to pyridine or mesitylene molecule.

Taking into account vicinity of the reaction center to the X substituent in 2-X-pyrazines, the isomer ratio may be presumed to be determined by both electronic and steric effects of the substituent. The difference in the inductive effects of alkyl groups in positions *2* and *3* of the pyrazine ring is likely to be insignificant, as follows from the existence of a correlation between the logarithms of the concentration ratio of cations **II** and **III** and steric constants of alkyl substituents (Table 3, Fig. 2).**

$$\log([\mathbf{II}]/[\mathbf{III}]) = (0.84\pm0.15)E_s^\circ - (0.19\pm0.07); \quad (1)$$
$$r = 0.96,\ s = 0.13,\ n = 5;$$

$$\log([\mathbf{II}]/[\mathbf{III}]) = -(0.41\pm0.03)F - (0.18\pm0.04); \quad (2)$$
$$r = 0.99,\ s = 0.06,\ n = 5.$$

In the general case, electronic effect of a substituent should be taken into consideration together with its steric effect. In fact, a broader series of substituents [X = H, Me, Et, Pr, *i*-Pr, MeCH(OH), H_2N, AcNH] gave rise to a multiparaameter correlation between the logarithms of the concentration ratio of *N*-aminopyr-

** The concentration of isomeric cation **IIf**, calculated by Eqs. (1) and (2), is 1 and 2%, respectively, which is consistent with the experimental data.

azinium cations and substituent constants σ_I, σ_R°, and E_s° (Table 3).

$$\log([\mathbf{II}]/[\mathbf{III}]) = -(0.24\pm0.08) + (0.87\pm0.98)\sigma_I - (1.03\pm0.60)\sigma_R^\circ + (0.94\pm0.11)E_s^\circ; \quad (3)$$
$$r = 0.98,\ s = 0.12,\ n = 8.$$

With a view to predict regioselectivity in the amination of substituted pyrazines we performed DFT/PBE/3z quantum-chemical calculations [28–30]. Transition states on the potential energy surface were identified by the presence of at least one imaginary frequency in the corresponding Hessian matrix, and the vibrational vector conformed to motion of the NH_2 group from the oxygen atom in the SO_3NH_2 group to the nitrogen atom in the pyrazine ring (Figs. 3, 4). Application of the internal reaction coordinate (IRC) procedure resulted in direct transition from the activated complex to the product or initial compound. Taking into account asymmetry of transition states, four different orientations of the reagent with respect to the substituent in the pyrazine ring were considered [X = Me, Et, Pr, *i*-Pr, MeCH(OH), NH_2, CN, Cl, MeO]. In all transition states found for 2-X-pyrazines, the interacting atoms N^1, $N(NH_2)$, and oxygen atom in the SO_3NH_2 group lie almost in one straight line (∠NNO 173–176°; Figs. 3, 4), which is typical of S_N2 reactions [31, 32]. The X substituent does not affect the N^1–$N(NH_2)$ and $O(SO_3)$–$N(NH_2)$ bond lengths to a considerable extent. All transition states are characterized by formation of hydrogen bond between hydrogen atom in the amino group and oxygen atom in the

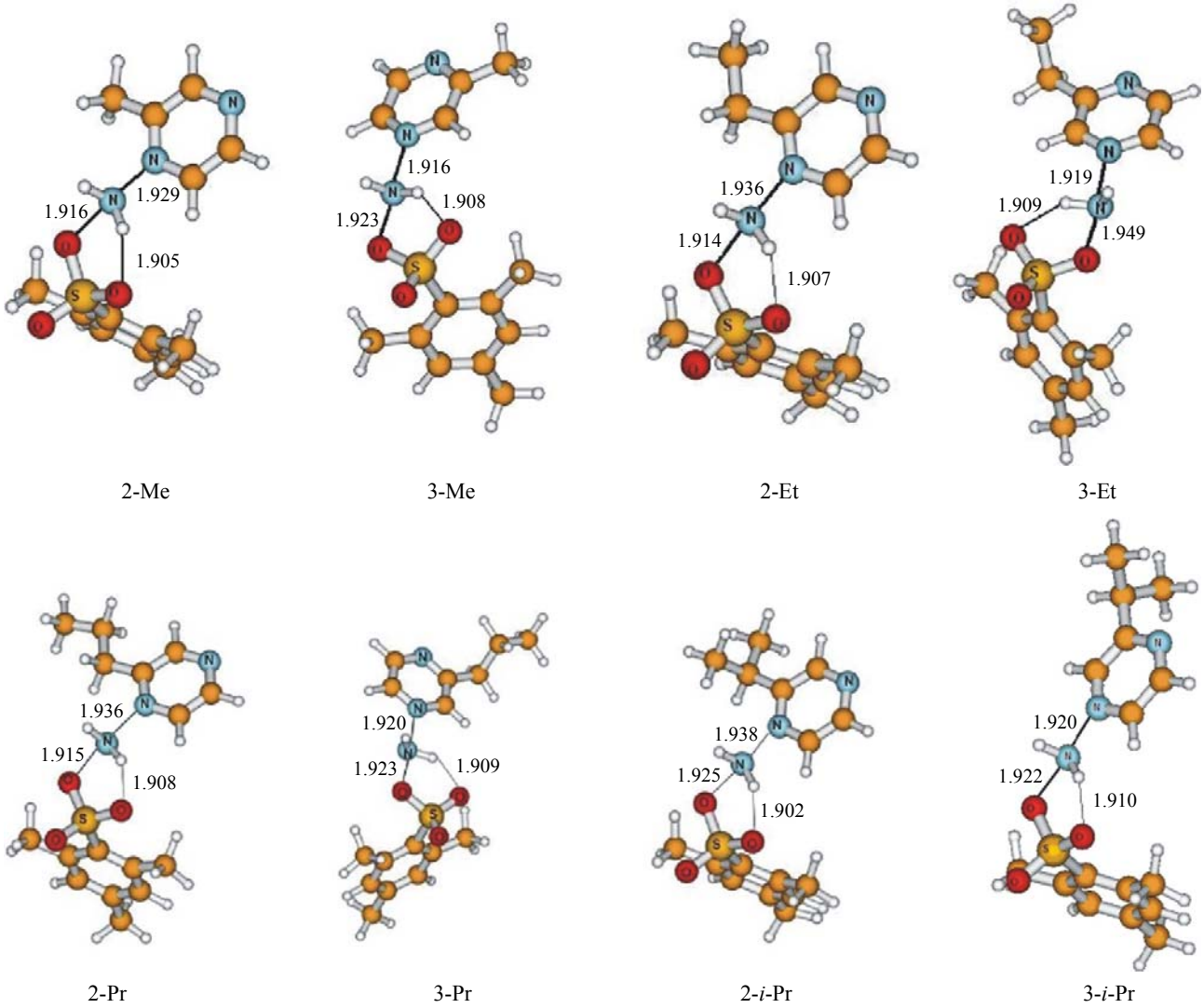


Fig. 3. Structures of transition states for the amination of 2-X-substituted pyrazines with *O*-mesitylenesulfonylhydroxylamine (X = Me, Et, Pr, *i*-Pr).

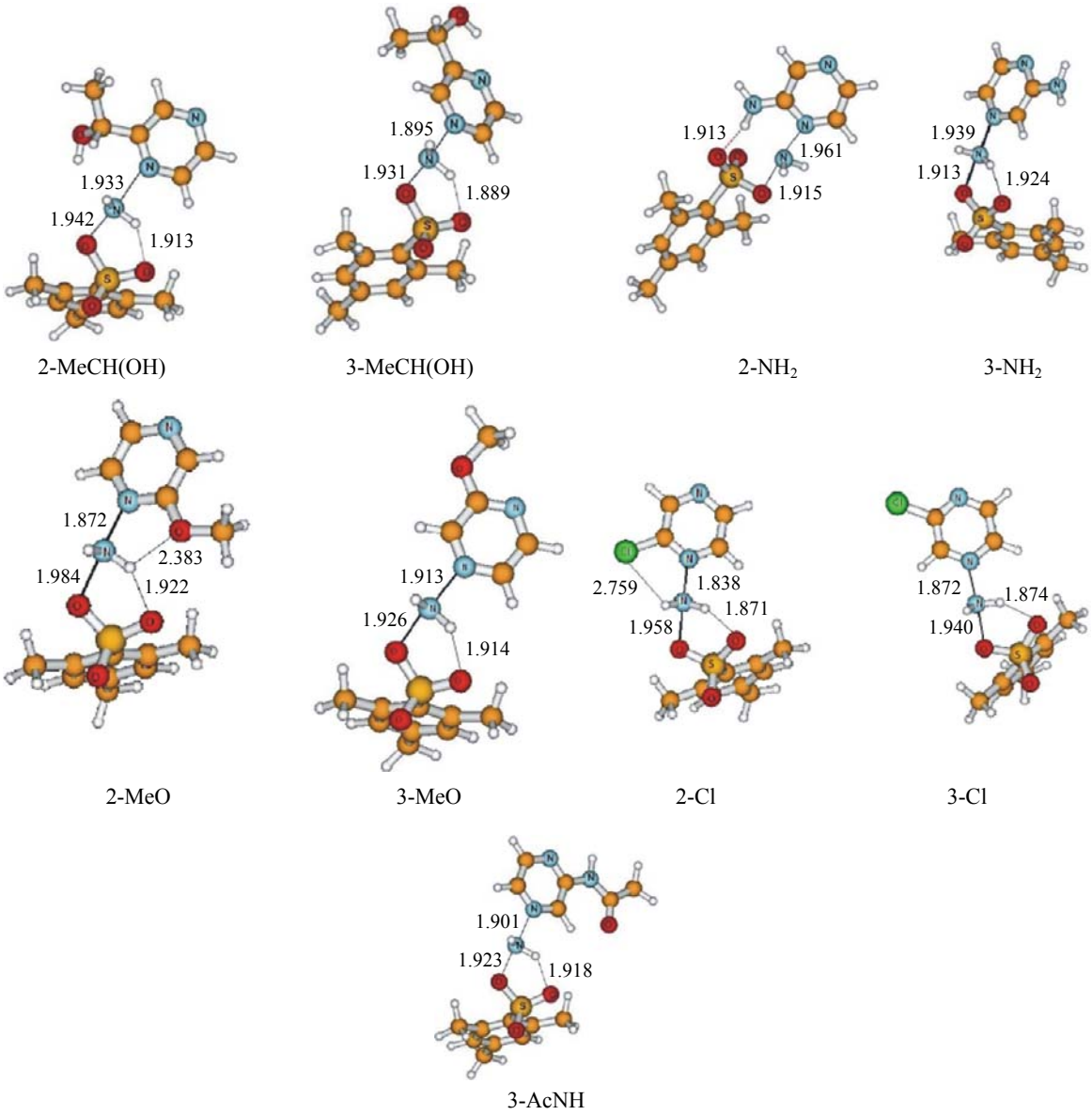


Fig. 4. Structures of transition states for the amination of 2-X-substituted pyrazines with *O*-mesitylenesulfonylhydroxylamine [X = MeCH(OH), H_2N, MeO, Cl, AcNH].

$MesSO_3$ group. Table 3 contains minimal energy barriers to the amination process.

Comparison of the log([**II**]/[**III**]) values with the calculated differences in the energies of activation for the formation of 2- and 3-substituted *N*-aminopyrazinium salts ($\Delta E^{\neq}$, Table 3) led to the following correlation:

$$\log([\mathbf{II}]/[\mathbf{III}]) = -(0.28\pm0.08) - (0.042\pm0.009)\Delta E^{\neq}_{calc}; \quad (4)$$
$$r = 0.91,\ s = 0.21,\ n = 7.$$

The calculations predicted formation of only one isomer, namely 3-substituted 1-aminopyrazinium ion, for 2-chloro- and 2-methoxypyrazines (X = Cl, MeO), which is consistent with the experimental data [22]. The difference in the calculated energies of activation for the formation of 2- and 3-substituted isomers is fairly large (13.4 and 20.9 kJ/mol, respectively). This may be due to unfavorable effect of unshared electron pairs on the chlorine or oxygen atom (in the methoxy group) which are not involved in *n*,π-conjugation with electron pairs on the oxygen atom in the OSO_2Mes group in the transition state corresponding to amination of 2-X-pyrazines at the N^1 atom. The calculated energy barriers to the amination of 2-cyanopyrazine at the nitrogen atoms in positions *1* and *4* ($E^{\neq}_{calc}$ = 77.0

and 79.5 kJ/mol, respectively) are much higher than those found for the other examined pyrazines (Table 3); this is consistent with our failure to obtain amination product from pyrazine **Ij** (X = CN).

Thus our results showed that the regioselectivity in the amination of 2-substituted pyrazines is determined by both electronic and steric effects of the substituent.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on Bruker AC-200, DRX-500, and AV-600 instruments at room temperature from solutions in DMSO-d_6 and $CDCl_3$ using the residual proton and carbon signals of the solvent as reference (DMSO-d_5, δ 2.50 ppm; DMSO-d_6, δ_C 39.50 ppm; $CHCl_3$, δ 7.24 ppm). Quantum-chemical calculations in terms of the density functional theory (DFT) using PBE functional [28] were performed with the aid of PRIRODA program [3z basis set; (11*s*6*p*2*d*)/(6*s*3*p*2*d*) and (5*s*1*p*)/(3*s*1*p*) for C, O, N, and S atoms and hydrogen atoms, respectively] [29, 30]. Critical points on the potential energy surface were identified by calculating the corresponding Hessian matrix [33]. The ^{1}H NMR spectra were calculated using Spinworks 2.5 program.

The following reagents and solvents were used: pyrazine (99%), 2-methylpyrazine (99%), pyrazin-2-carbonitrile (97%), pyrazin-2-amine (98%), 1-(pyrazin-2-yl)ethanone (99%) (Lancaster); 2-ethylpyrazine (98%), 2-propylpyrazine (>98%), isovaleric acid (99%), mesitylene (>98%) (Acros Organics); distilled isobutyric and pivalic acids of pure grade, DMSO-d_6 and $CDCl_3$ containing 99% of deuterium, and *O*-mesitylenesulfonylhydroxylamine [11]. Methylene chloride was purified according to the procedure described in [34] by washing with a saturated solution of sodium carbonate, followed by heating with activated charcoal under reflux, drying, and distillation over $CaCl_2$.

1-(Pyrazin-2-yl)ethanol (Ig) was synthesized by reduction of 2-acetylpyrazine [35]. ^{1}H NMR spectrum ($CDCl_3$, 200 MHz), δ, ppm: 1.54 d (3H, *J* = 7.0 Hz), 3.60 br.s, 4.97 q (1H, *J* = 7.0 Hz), 8.48 m (2H), 8.65 m (1H) (cf. [36]).

2-*tert*-Butylpyrazine (If) was synthesized as described in [37]. ^{1}H NMR spectrum ($CDCl_3$, 200 MHz), δ, ppm: 1.38 s (9H), 8.36 d (1H, *J* = 2.5 Hz), 8.48 d.d (1H, *J* = 2.5, 1.6 Hz), 8.64 d (1H, *J* = 1.6 Hz) (cf. [38]).

2-Isopropylpyrazine (Ie) was synthesized in a similar way. ^{1}H NMR spectrum ($CDCl_3$, 200 MHz), δ, ppm: 1.32 d (6H, *J* = 7.0 Hz), 3.08 sept (1H, *J* = 7.0 Hz), 8.36 m (1H), 8.46 m (2H) (cf. [38]).

***N*-(Pyrazin-2-yl)acetamide (Ii)** was synthesized as described in [39]. Colorless crystals, mp 132–133°C [40]. ^{1}H NMR spectrum (DMSO-d_6, 200 MHz), δ, ppm: 2.16 s (3H), 8.12 d.d (1H, *J* = 2.5, 1.5 Hz), 8.20 d.d (1H, *J* = 2.5, 0.9 Hz), 8.88 br.s (1H), 9.41 d.d (1H, *J* = 1.5, 0.9 Hz) (cf. [41, 42]).

2-Methyl-1,2,4-triazolo[1,5-*a*]pyrazine (IV). Yellow crystals, mp 130–132°C [43, 44]. ^{1}H NMR spectrum (200 MHz, $CDCl_3$), δ, ppm: 2.62 (3H), 9.14 d (1H, *J* = 2 Hz), 8.42 d.d (1H, *J* = 4.4, 2 Hz), 8.08 d (1H, *J* = 4.4 Hz) (cf. [44]).

General procedure for the amination of substituted pyrazines. Pyrazine **Ia**–**Ij**, ~0.5 mmol, was dissolved in 0.5 ml of methylene chloride, the solution was cooled to 0°C, and a solution of ~0.75 mmol of *O*-mesitylenesulfonylhydroxylamine in 1 ml of methylene chloride (preliminarily dried over sodium sulfate) was added dropwise under stirring. The mixture was stirred for 30 min at 0°C, allowed to warm up to room temperature, kept for 3 h, and diluted with 5 ml of diethyl ether. The precipitate was filtered off, washed with diethyl ether, and dried under reduced pressure. The overall yield of isomeric 2- and 3-substituted 1-aminopyrazinium salts **II** and **III** was 50–90%.

Evaluation of the kinetic stability of substituted 1-aminopyrazinium mesitylenesulfonates and of the possibility for NH_2 group transfer to bases. A ~0.1 M solution of 1-aminopyrazinium salt **IIh** or **IIIi** in DMSO was heated for 4 h at 100°C, and NMR spectra of the solution were recorded. Mesitylene or pyridine, 5 equiv, was added to a ~0.1 M solution of *N*-aminopyrazinium salt **IIa**, the mixture was heated for 3 h at 90°C, and its NMR spectra were recorded.

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