Kinetics and Mechanism of the Cyclization of Methyl (2-Cyano-4,6-dinitrophenylsulfanyl)acetate Producing Methyl 3-Amino-5,7-dinitrobenzo[*b*]thiophene-2-carboxylate

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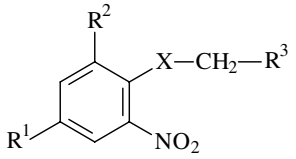
Base-catalyzed ring closure of methyl (2-cyano-4,6-dinitrophenylsulfanyl)acetate produces methyl 3-amino-5,7-dinitrobenzo[*b*]thiophene-2-carboxylate. This means that the carbanion initially formed attacks cyano group and not nitro group. The kinetics of this cyclization reaction has been studied in methanolic buffers of *tert*-amine/*tert*-ammonium chloride, and the reaction mechanism was suggested. The reaction is subject to general base catalysis. The found value of the Brønsted coefficient is $\beta = 0.9 \pm 0.1$, which indicates a late transition state of the rate-limiting proton transfer.

In recent years we have dealt with kinetics and mechanisms of intramolecular reactions of carbanions having an electron-deficient centre, most frequently a nitro group. The nucleophilic attack on nitrogen atom of the nitro group proceeds easily in such cases, when the intramolecular reaction can produce five- or six-membered rings. The nucleophilic species involve carbanions, reactive aromatic rings, or amino groups [1]. The ring-closure reaction of *o*-substituted nitroarenes, involving the condensation reaction between nitro group and nucleophilic centre at the *ortho*-standing substituent, can be considered a standard way of preparation of various heterocyclic *N*-oxides (nitrones) [2]. The reaction proceeds under mild conditions and with good yields if the formation of the carbanion is facilitated by an activating group (a strong electron-acceptor group) such as carbonyl [3], nitrile [4, 5], ester [6, 7], or amide group [8]. Activation by weak electron-acceptor groups, such as *e.g.* aryl groups, necessitates application of strong bases: hydroxide, alkoxide, or hydride ions [9].

It was found that the structure of the product formed also depends on the nature of the bridge atom X (Formula 1) connecting the aromatic and aliphatic moieties and on a potential presence of another nitro group in the benzene ring. Earlier we studied reactions of methyl *N*-(2,4,6-trinitrophenyl)aminoacetate [10] and methyl *N*-methyl-*N*-(2,4,6-trinitrophenyl)aminoacetate (X = NR) [11] with methoxide ion in methanol, and we found that the reaction does not consist in a cyclization to the corresponding *N*-oxide but in a reduction of *ortho*-standing nitro group to nitroso group with concomitant oxidation of the side chain and its elimination. The reaction of methyl *N*-(2,4-dinitrophenyl)aminoacetate [12] leads to deeper reduction giving 5-nitrobenzimidazol-2(3*H*)-one. If the bridge atom is oxygen (X = O) and the base adopted is sodium methoxide, the ring closure to the respective *N*-oxide does not proceed either, the final product being 1,1-dimethoxy-2,4-dinitrocyclohexadienide or 1,1-dimethoxy-2,4,6-trinitrocyclohexadienide, respectively [13]. The ring closure with the bridge atom of sulfur (X = S) gives the respective substituted benzothiazole-*N*-oxide even in such cases where one of the *ortho*-positions is occupied by a nitro group and the other by an alkyl group [14], halogen [14] or another nitro group [15] (Scheme 1). The parent 2,4-dinitro derivative does not undergo ring closure. Different behaviour was also observed in the case of the 2-methoxycarbonyl derivative [14], when the reaction gave – instead of the expected *N*-oxide



R^1, R^2 = H, NO_2 X = N, O, S
R^3 = CN, $COOCH_3$, $CONH_2$, Ar

Formula 1

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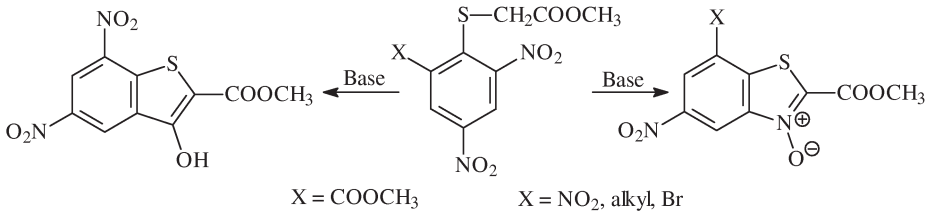
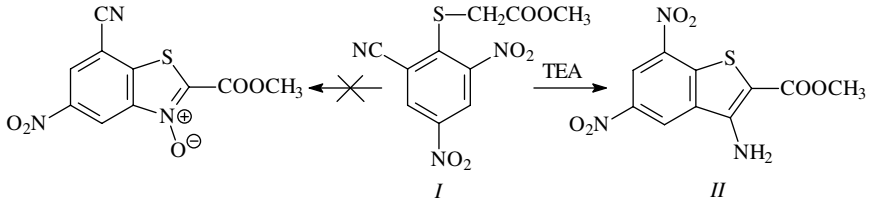


Scheme 1



Scheme 2

– a product of attack at methoxycarbonyl group, *i.e.* the Dieckmann condensation product: methyl 3-hydroxybenzo[*b*]thiophene-2-carboxylate.

This paper deals with the behaviour of analogous methyl (2-cyano-4,6-dinitrophenylsulfanyl)acetate (*I*), which in principle can undergo two different ring-closure reactions, *viz.* by nucleophilic attacks at nitro group or at cyano group (Scheme 2).

EXPERIMENTAL

The buffer solutions were prepared from *N*-methylmorpholine (NMF, 99 % Aldrich), *N*-methylpiperidine (NMP, 99 % Aldrich), and triethylamine (TEA, 99.6 % Merck), which were dried over potassium hydroxide pellets and distilled. The pK_a values of *N*-methylmorpholinium, triethylammonium, and *N*-methylpiperidinium in methanol at the ionic strength I = 0.1 mol dm^{-3} at 25 °C were determined spectrophotometrically from the absorbances of 2-chloro-4-nitrophenol and 4-nitrophenol as the indicators.

The ^{1}H and ^{13}C NMR spectra were measured with a BRUKER AVANCE 500 spectrometer at the frequencies of 500.13 MHz (^{1}H) and 125.77 MHz (^{13}C) in deuteriochloroform ($CDCl_3$). The chemical shift $\delta(^1\mathrm{H})$ was referenced to the signal of hexamethyldisiloxane ($\delta(^1\mathrm{H}) = 0.05$), and $\delta(^{13}\mathrm{C})$ to the middle signal of the solvent ($\delta(^{13}\mathrm{C}) = 77.0$). The assignment of signals in ^{13}C NMR spectrum was carried out by the ^{1}H—^{13}C HSQC and ^{1}H—^{13}C HMBC techniques. The kinetic measurements were performed on an HP UV/VIS 8453 Diode Array spectrophotometer in 1 cm quartz cell of 2 cm^3 volume, placed in thermostat block of the apparatus kept at 25 °C. The reactions having half-lives shorter than about 2 s were followed by means of a Diode Array Stopped-Flow spectrophotometer SX.18MV-R (produced by Applied Photophysics) in a 1 cm cell of 20 mm^3 volume, kept at the temperature of 25 °C.

Methyl (2-Cyano-4,6-dinitrophenylsulfanyl)-acetate (*I*)

A 250 cm^3 three-necked flask filled with inert gas was charged with 2-chloro-3,5-dinitrobenzonitrile (2.5 g; 11 mmol) and 1,2-dimethoxyethane (80 cm^3). Within 1 h at room temperature, a solution containing triethylamine (1.5 cm^3, 11 mmol), 1,2-dimethoxyethane (94 cm^3), and methyl sulfanylacetate (1 cm^3, 11 mmol) was added drop by drop, and the mixture was stirred for another 1.5 h. After the reaction was finished, the mixture was poured into 80 cm^3 of 5 % hydrochloric acid and then extracted with 3 × 150 cm^3 of dichloromethane. The organic layer was dried and the dichloromethane was distilled off at room temperature. The raw product (2.4 g) was suspended in 40 cm^3 of chloroform, the insoluble part was filtered off and the filtrate evaporated until dry to obtain 1.55 g (48 %) of the product, m.p. = 54—56 °C. ^{1}H NMR spectrum ($CDCl_3$), δ: 3.95 (s, 2H, CH_2), 3.68 (s, 3H, CH_3), 8.69 (d, 1H, $^4J_{3,5}$ = 2.4 Hz, H-3), 8.78 (d, 1H, H-5). ^{13}C NMR spectrum, δ: 167.8 (CO), 154.2 (C-6), 146.9 (C-4), 140.1 (C-1), 130.8 (C-3), 122.6 (C-5), 121.8 (C-2), 114.2 (CN), 53.1 (CH_3), 36.8 (CH_2). Elemental analysis, w_i(calc.): 40.41 % C, 2.37 % H, 14.14 % N, 10.79 % S; w_i(found): 40.21 % C, 2.29 % H, 14.27 % N, 10.98 % S.

Methyl 3-Amino-5,7-dinitrobenzo[*b*]thiophene-2-carboxylate (*II*)

A 100 cm^3 three-necked flask placed on a water bath (40 °C) was charged with *I* (0.5 g; 1.8 mmol) and 1,2-dimethoxyethane (25 cm^3). With stirring, the mixture was treated with triethylamine (0.25 cm^3, 1.8 mmol) in 1,2-dimethoxyethane (10 cm^3) added drop by drop. After adding all the triethylamine, the solution was stirred for another 15 min. After the reaction was finished, the mixture was poured into 80 cm^3

of 5 % hydrochloric acid and then extracted with 2 × 40 cm^3 of dichloromethane. The organic layer was dried and the dichloromethane was distilled off in vacuum. The raw product was recrystallized from benzene. Yield 0.3 g (58 %), m.p. = 255.5—257 °C. ^{1}H NMR spectrum ($CDCl_3$), δ: 3.95 (s, 3H, CH_3), 6.10 (bs, 2H, NH_2), 8.89 (d, 1H, $^4J_{6,8}$ = 1.9 Hz, H-4), 9.31 (d, 1H, H-6). ^{13}C NMR spectrum ($CDCl_3$), δ: 164.2 (CO), 149.4 (C-3), 144.5 (C-5), 141.9 (C-7), 138.5 (C-7a), 134.6 (C-2), 125.3 (C-4), 119.8 (C-6), 99.1 (C-3a), 52.1 (CH_3). Elemental analysis, w_i(calc.): 40.41 % C, 2.37 % H, 14.14 % N, 10.79 % S; w_i(found): 40.58 % C, 2.18 % H, 14.39 % N, 10.57 % S.

RESULTS AND DISCUSSION

The synthesized *I* is very sensitive to bases and heating. At enhanced temperatures and/or by action of bases it undergoes ring closure to give *II*. The latter substance is formed in a yield of *ca.* 25 % already during the preparation of *I* and can be separated as a portion less soluble in chloroform. Due to its instability, the substance *I* could not be purified by recrystallization from hot solutions.

The ring closure could also produce 2-methoxycarbonyl-7-cyano-5-nitrobenzo[*d*]thiazol-3-oxide (*i.e.* the product of attack at nitro group – Scheme 2), but the results of both elemental analysis and NMR spectroscopy showed that the only cyclization product is *II*. This finding agrees with the fact that the cyano group represents a better substrate than the nitro group for a nucleophilic attack.

The ring-closure kinetics of *I* was studied in methanolic solutions of tertiary amine buffers at the conditions of the pseudo-first-order reaction ($c = 10^{-4}$ mol dm^{-3}). The spectral records (Fig. 1) show well-developed isosbestic points, which means that neither any consecutive reactions make themselves felt nor any traceable intermediate is formed. Comparison of electronic spectrum of reaction mixture after cyclization with that of the reaction product of ring closure in the same solvent at the same concentration showed that they were identical.

In order to determine the type of acid-base catalysis, series of measurements were carried out in methanolic buffers prepared from NMF, NMP, and TEA with varying ratios $x_r = [B]/[BH^+]$ of acid and basic components and varying concentration of buffer at constant ionic strength $I = 0.1$ mol dm^{-3} adjusted by addition of sodium perchlorate. These measurements for each buffer gave series of parallel straight lines with positive slopes (Figs. 2 and 3), which means that the ring-closure reaction is subject to general base catalysis with rate-limiting splitting of C—H bond. On the basis of the facts found it is possible to suggest the below-given mechanism (Scheme 3).

The first step involves deprotonation of the methylene group with adjacent sulfur atom and carbonyl

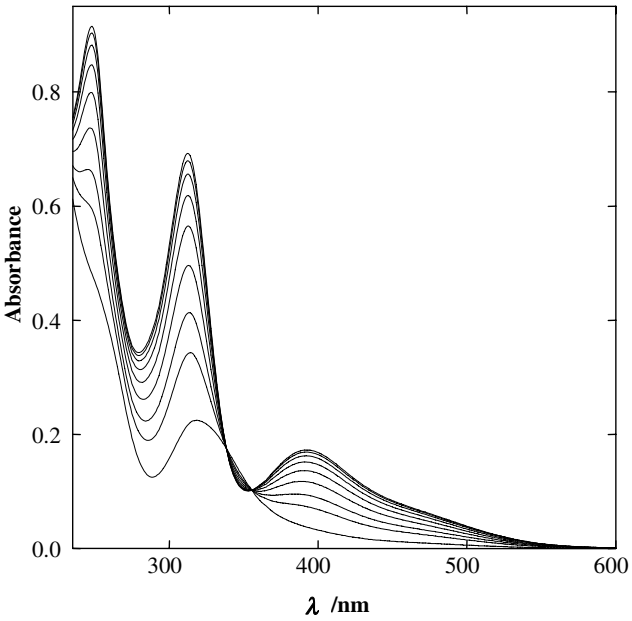


Fig. 1. Spectral record of the course of reaction $I \rightarrow II$ at the concentration $[I] = 10^{-4}$ mol dm^{-3} in NMF buffer at $x_r = 4:1$ at 25 °C.

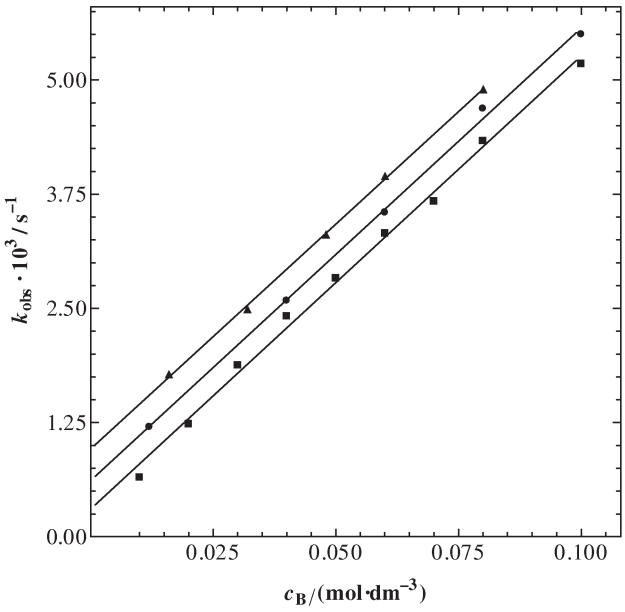


Fig. 2. Dependence of observed rate constant, k_{obs}, of ring closure of *I* on concentration c_B of the basic component of NMF buffer at x_r = 1:1 (■), 2:1 (●), 4:1 (▲).

group. The anion thus formed is stabilized by both the resonance and *d* orbitals of sulfur [16] and attacks – as a nucleophile – the nitrile group to give the cyclic, negatively charged intermediate In_1^-. Theoretically, this cyclic intermediate can react further in two ways: one involves its fast reaction with solvent or with the conjugated acid of the applied base thus giving the neutral intermediate In_1, which in subsequent step is again deprotonated at the carbon atom, the interme-

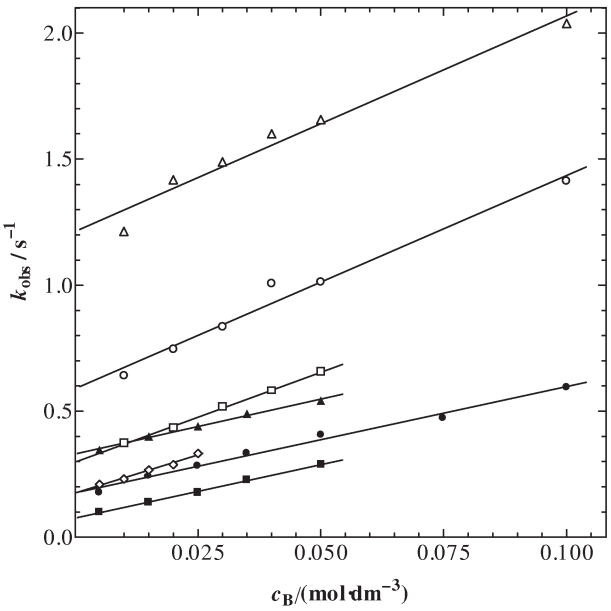


Fig. 3. Dependence of observed rate constant, k_{obs}, of ring closure of *I* on concentration c_B of the basic component of NMP buffer at $x_r = 1{:}1$ (■), 2:1 (●), 4:1 (▲) and TEA buffer at $x_r = 1{:}2$ (◇), 1:1 (□), 2:1 (○), 4:1 (△).

diate formed (In_2^-) rapidly giving the product. The other possibility of formation of intermediate In_2^- consists in a synchronous solvent-mediated proton switch [17]. This synchronous process could be favourable especially due to the fact that the proton transfer proceeds through an advantageous six-membered cycle. This reaction pathway makes itself felt with amines [18]. However, since conjugated base of imine is probably weaker base as compared with amines (two nitro groups on benzene ring acidify imino group), this possibility is less likely.

The rate-limiting step of the reaction is splitting of C—H bond. In the mechanism presented, such splitting occurs twice: the first is the deprotonation of *I*, the second is deprotonation of intermediate In_1. The hydrogen atom in intermediate In_1 is much more acidic than that in the starting substrate, because the formed intermediate In_2^- is stabilized not only by resonance with the carbonyl group and with *d* orbitals of the sulfur atom, but also by the imine group present. Therefore, its deprotonation is fast [19]. That is why we presume the rate-limiting step to consist in the formation of the anion of substrate *I*. The same finding was published [15] in the case of cyclization of methyl (2,4,6-trinitrophenylsulfanyl)acetate, where it was unambiguously proved by means of deuteration that the formation of substrate anion is rate-limiting. In addition, the step connected with the splitting off of the second proton forms a part of tautomeric transformation between imino and enamino derivatives. Such tautomeric transformations are in most cases fast [19].

The kinetic data obtained were evaluated on the basis of eqn (*1*), which is valid for reactions subject to general base catalysis. The slopes of straight-line dependences in Figs. 2 and 3 determine the constant of general catalysis k_B for the base in the given buffer.

$$k_{obs} = k_0 + k_B[B] + k_{CH_3O^-}[CH_3O^-] \qquad (1)$$

Extrapolation to zero buffer concentration gave the corresponding k_{ext} values which include the constant $k_{CH_3O^-}$ and the constant k_0 for noncatalyzed or solvent-catalyzed reaction. The values of k_B are presented in Table 1 along with the k_{ext} values.

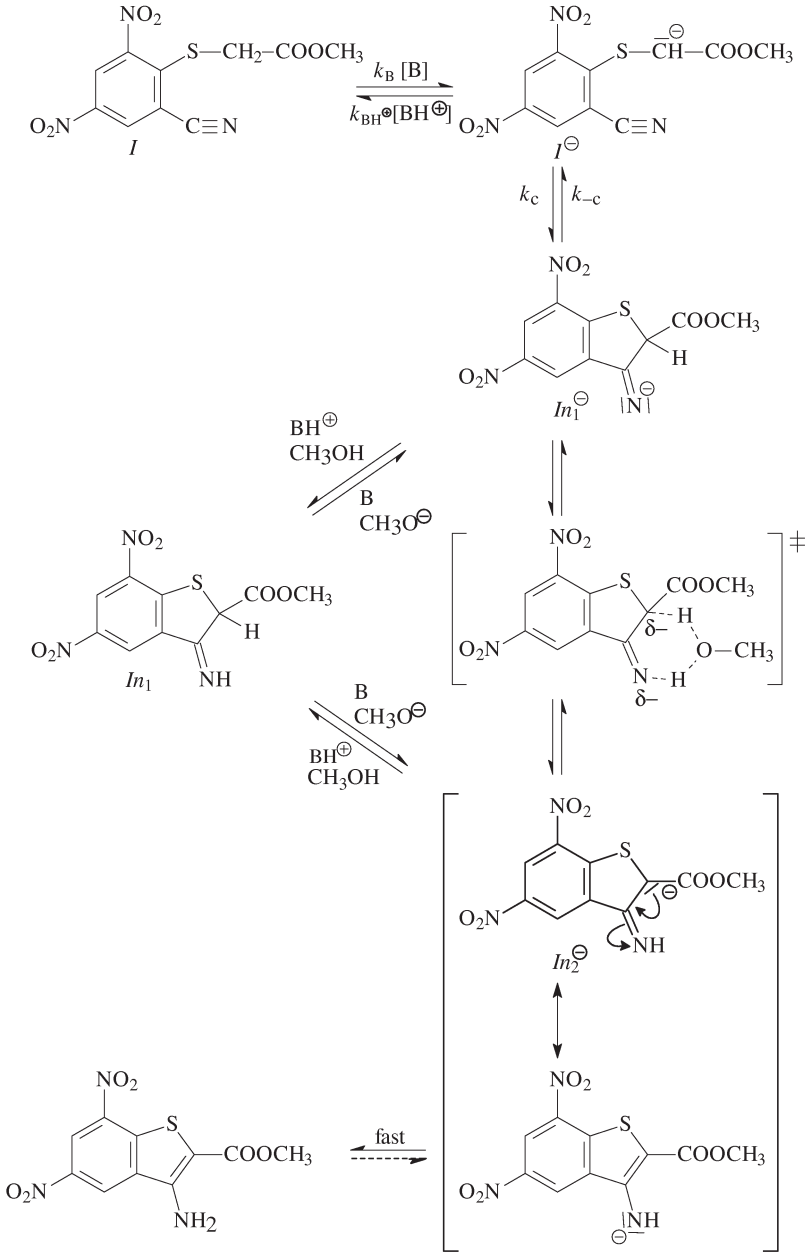
From Table 1 it can be seen that the rate constants of general base catalysis, k_B, increase with increasing pK_a value of the given buffer. The Brønsted dependence of $\log k_B$ *vs.* pK_a is linear eqn (*2*). From its slope it is possible to estimate the structure of the transition state of the rate-limiting step. The value found by us, $\beta = 0.9 \pm 0.1$, indicates a late transition state, which means that the proton is more than 90 % bound to the base in the transition state.

$$\log\{k_B\} = -\beta \log K_a + C \qquad (2)$$

This stands in accordance with the presumption that the pK_a value of the starting substrate is very

Table 1. Values of Catalytic Constants k_B and k_{ext} Determined in Individual Buffers and pK_a Values of the Protonated Amine Bases

Buffer	pK_a	x_r [B]/[BH$^+$]	k_B/(dm^3 mol^{-1} s^{-1})	$10^2 \cdot k_{ext}$/s^{-1}
NMF	9.06	1:1	0.0498	0.0205
		2:1	0.0496	0.0303
		4:1	0.0493	0.0959
NMP	10.94	1:1	4.24	7.54
		2:1	4.22	17.6
		4:1	4.35	33.0
TEA	11.60	1:2	6.05	17.5
		1:1	7.12	29.7
		2:1	8.46	58.9
		4:1	8.58	121



Scheme 3

high, being much higher than the pK_a values of the buffers used in the measurements. The pK_a value of substrate can be estimated on the basis of linear free energy relationships (LFER) in the following way. The pK_a value of Ph—S—CH_2—COOEt in dimethyl sulfoxide is 21.2 [20]. The effect of change of medium when going from dimethyl sulfoxide to methanol can be estimated from the values of pK_a of NC—CH_2—COOMe in methanol [21] (pK_a = 15.19) and pK_a of NC—CH_2—COOEt in dimethyl sulfoxide [22] (pK_a = 13.10). The pK_a value of Ph—S—CH_2—COOEt in methanol, estimated from the values given, is about 23.3. The effect of two nitro groups and one cyano group in methyl (2-cyano-4,6-dinitrophenylsulfanyl)acetate (*I*) can be calculated from the equation

$$\mathrm{p}K_a \cong \mathrm{p}K_a(\mathrm{Ph—S—CH_2—COOEt}) - \\ -(\rho_p\sigma_p^{NO_2} + \rho_o\sigma_o^{NO_2} + \rho_o\sigma_o^{CN}) \qquad (3)$$

The ρ constant for the given substrate is known from literature [15]: $\rho = 2.15$. The σ values were taken from Ref. [23]. The estimate obtained by introducing these values into eqn (*3*) is pK_a = 18.3.

The values of intercepts obtained by extrapolation to zero buffer concentration (k_{ext}) make it possible to find also the rate constant of catalysis by methoxide ion, which is present in the buffer solution at an

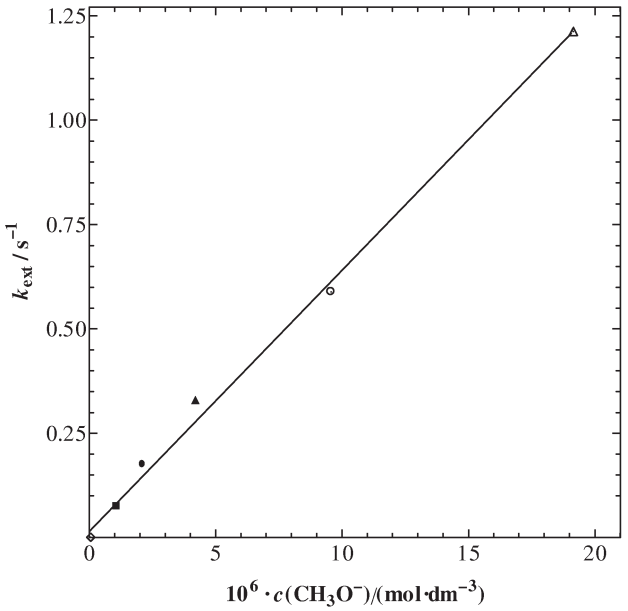


Fig. 4. Dependence of extrapolated rate constant, k_{ext}, on concentration of methoxide in NMF at $x_r = 4{:}1$ (◊), NMP at $x_r = 1{:}1$ (■), 2:1 (●), 4:1 (▲), and TEA at $x_r = 2{:}1$ (○), 4:1 (△).

equilibrium concentration, and, as the case may be, also the rate constant k_0 of the noncatalyzed reaction. The evaluation was carried out by plotting the extrapolated k_{ext} values obtained from a series of NMF, NMP, and TEA buffers against the equilibrium concentration of methoxide ion given by eqn (*4*). The autoprotolytic constant of methanol pK_{CH_3OH} = 16.92 [24].

$$[CH_3O^-] = \frac{K_{CH_3OH}}{K_a} \cdot \frac{[B]}{[BH^+]} \qquad (4)$$

In this way we obtained again a linear dependence (Fig. 4) the slope of which gives the rate constant $k_{CH_3O^-}$ and the intercept gives the k_0 value. Since the intercept at *y*-axis (k_0) is statistically insignificant, the noncatalyzed reaction does not make itself felt. The value of $k_{CH_3O^-} = (6.30 \pm 0.02) \times 10^4$ dm^3 mol^{-1} s^{-1} is by 4 orders higher than k_B corresponding to individual amine buffers, which agrees with the fact that methoxide anion is a *ca.* by 5—6 orders stronger base than are the amines used in the buffers.

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