Generation and trapping of cyclopropyldiazonium and diazocyclopropane in the nitrosation of cyclopropylamine with alkyl nitrites*

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Diazocyclopropane and an cyclopropyldiazonium ion, which are highly reactive intermediates, can be generated and trapped by appropriate substrates immediately in the direct nitrosation of cyclopropylamine with alkyl nitrites. Diazocyclopropane is trapped by unsaturated compounds to form the corresponding 1,3-dipolar cycloadducts, while cyclopropyldiazonium reacts with reactive arenes and CH acids (*e.g.*, malononitrile) to give azo compounds. It was shown that both cyclopropyldiazonium and diazocyclopropane in equilibrium can be simultaneously trapped in the presence of equimolar amounts of 2-naphthol and acrylonitrile or methyl methacrylate.

Key words: diazocyclopropane, cyclopropyldiazonium, azo coupling, 1,3-dipolar cycloaddition, cyclopropylazoarenes, cyclopropylhydrazones.

Direct diazotization of aromatic amines is known to afford diazonium salts, which are widely used in azo coupling reactions. In contrast, diazonium ions generated in diazotization of aliphatic amines are very unstable and easily give carbocations through the loss of nitrogen, which undergo further conversions.[2,3] Nevertheless, for some alkyldiazonium ions, azo coupling can successfully compete with deazotization processes.[4] For instance, we showed that cyclopropyldiazonium ion (**1**) generated by alkaline hydrolysis of *N*-cyclopropyl-*N*-nitrosourea can be involved in azo coupling. With some reactive arenes (*e.g.*, naphthols) as scavengers for diazonium ions **1**, the corresponding cyclopropylazoarenes[5] were obtained, while the use of aliphatic CH acids, which contain an activated methylene group, affords the corresponding cyclopropylhydrazones.[6]

In addition, we recently[1] found that cyclopropyldiazonium ion **1** generated in the nitrosation of cyclopropylamine with isoamyl nitrite can enter into azo coupling reactions with 1- and 2-naphthols.

In the present work, we studied in more detail the generation of cyclopropyldiazonium **1** in the nitrosation of cyclopropylamine with alkyl nitrites (in particular, in the presence of 8-hydroxyquinoline and some CH acids) and demonstrated that diazocyclopropane (**2**) can be generated under these conditions to give 1,3-dipolar cycloadducts in reactions with olefins.

Under normal conditions, cyclopropylamine does not react with *n*-butyl or isoamyl nitrite. The ^{1}H NMR spectrum of a mixture of cyclopropylamine and *n*-butyl nitrite in $CDCl_3$ shows signals for the starting compounds only (5 °C, 16 h). However, addition of 1- or 2-naphthol under the same conditions gives rise to cyclopropylazonaphthols **3**—**6** through the generation of cyclopropyldiazonium **1** and its azo coupling with the naphthols (Scheme 1). Apparently, cyclopropylamine reacts with alkyl nitrites activated by naphthols, which exhibit weak acid properties.

With special experiments,[1] we showed that azo compounds **3**—**6** cannot alternatively form through the nitrosation of naphthols with alkyl nitrites followed by reactions of the corresponding nitroso compounds with cyclopropylamine. Indeed, although isoamyl nitrite reacts with 2-naphthol in $CHCl_3$ at 5 °C, this reaction is nonselective and no nitroso compound **7** was detected among the reaction products (^{1}H NMR data). However, we found that nitrosonaphthol **7** itself (synthesized according to a known procedure[7]) slowly reacts with cyclopropylamine in $CHCl_3$ to give, *via* its oxo imine form, compound **8** rather than isomeric azo derivative **3** (5 °C, 16 h, **7** : **8** = 5.6 : 1) (Scheme 2).

In fact, the reaction mechanism includes the nitrosation of cyclopropylamine (as part of associates with naphthols) with alkyl nitrite followed by the azo coupling of cyclopropyldiazonium with reactive 1- and 2-naphthols to give cyclopropylazonaphthols. Nitrosation of the starting naphthols is also possible as a side process; however, this reaction is not responsible for the formation of the corresponding azo compounds.

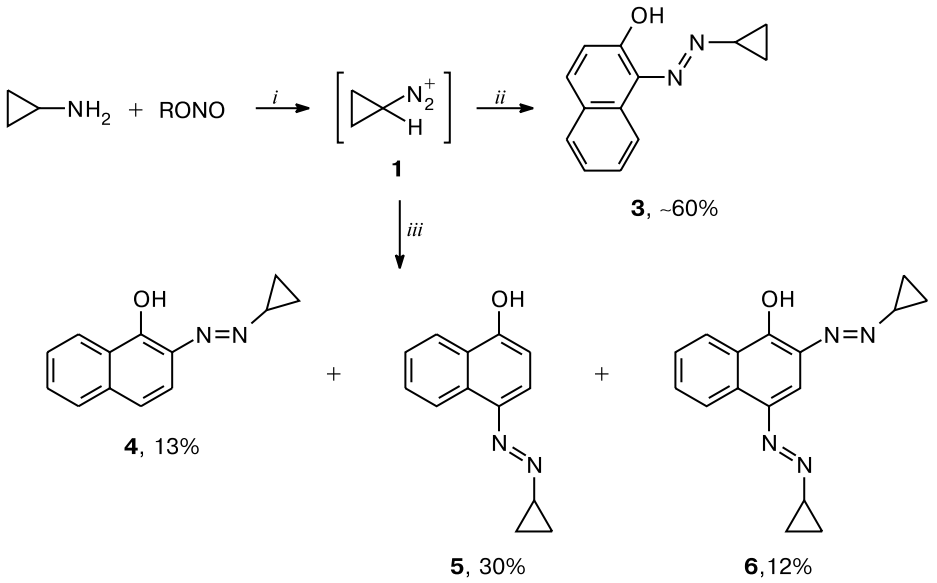
It should be noted that under analogous conditions ($CHCl_3$, 5 °C) in the presence of 8-hydroxyquinoline, no nitrosation of cyclopropylamine with isoamyl nitrite oc-

* For the preliminary communication, see Ref. 1.

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 3, pp. 640—644, March, 2004.

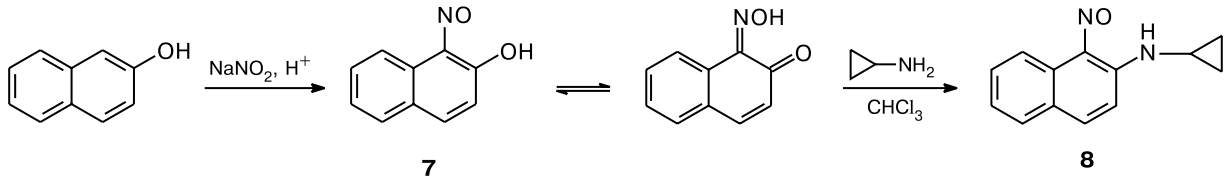
1066-5285/04/5303-0671

Scheme 1



Conditions: *i*. Weak acid. *ii*. 2-Naphthol. *iii*. 1-Naphthol.

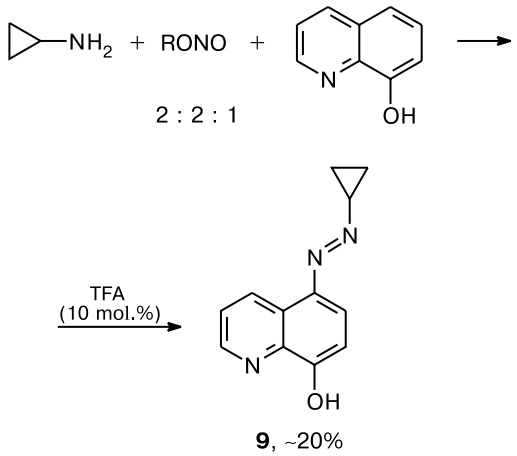
Scheme 2



curs even over several days, and the ^{1}H NMR spectrum shows signals for the starting compounds only. However, in the presence of 10 mol. % TFA (5 °C, 15 h), this reaction affords 5-(cyclopropylazo)-8-hydroxyquinoline (**9**) in ~20% yield. This compound is identical with that isolated by us earlier[5] when cyclopropyldiazonium **1** was generated by decomposition of *N*-cyclopropyl-*N*-nitrosourea with K_2CO_3 (Scheme 3). This result suggests an important role of the acidity of the medium in the nitrosation of cyclopropylamine with alkyl nitrites; however, a significant decrease in pH can provoke irreversible formation of the corresponding cyclopropylammonium salt.

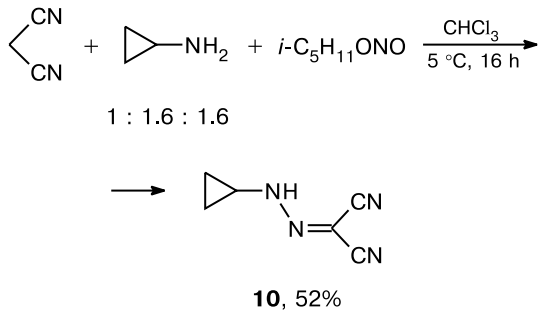
Being a reactive CH acid, malononitrile can react with cyclopropyldiazonium to give azo compounds. The reaction of isoamyl nitrite with a mixture of cyclopropylamine and malononitrile in $CHCl_3$ affords the expected cyclopropylhydrazone **10** (Scheme 4). Its yield is comparable with the yield (56%) obtained in an analogous reaction of ion **1** generated by decomposition of *N*-cyclopropyl-*N*-nitrosourea with K_2CO_3 (see lit.[6]). This method is inapplicable to pentane-2,4-dione because of its rapid reaction with cyclopropylamine.

Scheme 3



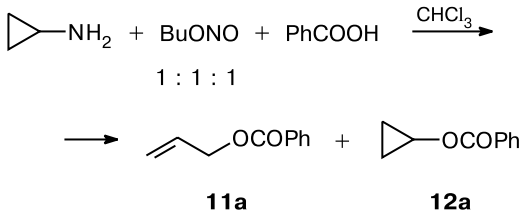
In the absence of efficient scavengers, cyclopropyldiazonium **1** is easily deazotized to give cyclopropyl and allyl esters of the acids employed for activation of alkyl nitrites. For instance, when an equimolar mixture of

Scheme 4



cyclopropylamine, *n*-butyl nitrite, and benzoic acid is kept in $CDCl_3$ at 5 °C for 16 h, the total yield of allyl (**11a**) and cyclopropyl benzoates (**12a**) is 60% (**11a** : **12a** ≈ 4 : 1) (Scheme 5).

Scheme 5



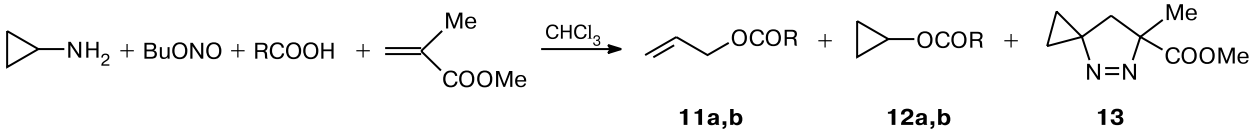
Earlier,[6] we demonstrated that the alkaline hydrolysis of *N*-cyclopropyl-*N*-nitrosourea allows simultaneous generation and trapping of both cyclopropyldiazonium **1** (*e.g.*, as azo compounds) and diazocyclopropane **2** (as products of 1,3-dipolar cycloaddition to unsaturated compounds). In connection with this, it was interesting to study the possibility of generating diazocyclopropane in the nitrosation of cyclopropylamine with alkyl nitrites and simultaneous trapping of intermediates **1** and **2** by appropriate substrates.

Addition of methyl methacrylate as a scavenger for diazocyclopropane **2** to a equimolar mixture of cyclopropylamine and *n*-butyl nitrite in the presence of benzoic acid (10 mol. %) affords 6-methoxycarbonyl-6-methyl-4,5-diazaspiro[2.4]hept-4-ene (**13**)[8] in up to 60% yield (5 °C, 11 days). The reaction does not occur without benzoic acid; when its equimolar amount is used, the yield of pyrazoline **13** is low, although the reaction is completed within two days. In this case, the major reaction products are esters **11a** and **12a** (Scheme 6). According to the ^{1}H NMR data, the ratio between **11a**, **12a**, and **13** is 7.6 : 6 : 1; *i.e.*, as expected, an increase in the acid content favors deazotization rather than 1,3-dipolar addition of diazocyclopropane to methyl methacrylate. Interestingly, in the presence of an equimolar amount of pivalic acid under the same conditions, the yield of pyrazoline **13** is 24% (*vs.* ~7 % with benzoic acid), while the ratio of allyl (**11b**) and cyclopropyl (**12b**) pivalates to pyrazoline **13** is ~1.3 : 0.9 : 1, respectively.

The use of methyl acrylate as a scavenger for diazocyclopropane **2** generated from cyclopropylamine and isoamyl nitrite in the presence of benzoic acid (10 mol. %) also gives a target product, namely, 6-methoxycarbonyl-4,5-diazaspiro[2.4]hept-5-ene (**14**);[9] however, the major product is methyl 3-(cyclopropylamino)propionate (**15**) (Scheme 7) formed as a result of the Michael addition[10] of cyclopropylamine to methyl acrylate (**14** : **15** ≈ 1 : 1.4).

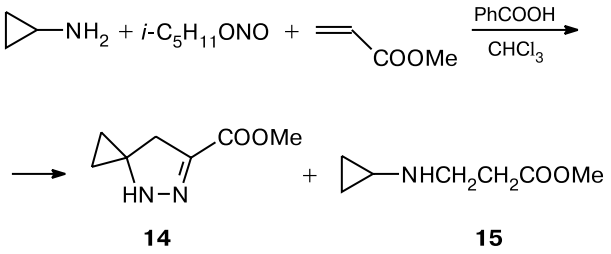
The formation of pyrazolines **13** and **14** is strong evidence for the generation of diazocyclopropane in the nitrosation of cyclopropylamine with alkyl nitrites. Depending on the substrate nature, both diazocyclopropane and cyclopropyldiazonium ion can be trapped. Trapping of both intermediates under the same conditions (5 °C, 13—16 h, $CHCl_3$) was detected in the reaction cyclopropylamine with isoamyl nitrite in the presence of equimolar amounts of 2-naphthol and methyl methacrylate or acrylonitrile. In both cases, the formation of azo compound **3** is accompanied by 1,3-dipolar cycloaddition of diazocyclopropane **2** to the unsaturated compounds to give pyrazoline **13** or 6-cyano-4,5-diazaspiro[2.4]hept-5-ene (**16**). The latter was previously synthesized[9] by the reaction of acrylonitrile with diazocyclopropane **2** generated by alkaline hydrolysis of *N*-cyclopropyl-*N*-nitrosourea. In the reactions studied, the ratio between compounds **3** and **16** is ~1 : 1.7 and that between compounds **3** and **13** is ~4 : 1 (^{1}H NMR data), which correlates with the higher reactivity of acrylonitrile compared to methyl methacrylate. Note that the ratio between compounds **3** and **13** is ~22 : 1 when intermediates **1** and **2** are generated by alkaline hydrolysis of *N*-cyclopropyl-*N*-nitrosourea in the presence of 2-naphthol and methyl methacrylate.[11] Apparently, the reason for such a difference is that in the nitrosation of cyclopropylamine with alkyl nitrites,

Scheme 6



R = Ph (**a**), CMe_3 (**b**)

Scheme 7



14 **15**

diazonium **1** reacts with 2-naphthol itself, while in the second case, more reactive naphtholate anions are involved.

Thus, we showed for the first time that cyclopropyldiazonium ions can be generated by the reactions of cyclopropylamine with alkyl nitrites in the presence of some weak protonating reagents and trapped in azo coupling. Malononitrile and 1- and 2-naphthols are reactive substrates in this reaction; in the case of 8-hydroxyquinoline, an acid (*e.g.*, 10 mol. % TFA) is required. The presence of reactive unsaturated compounds (*e.g.*, acrylonitrile or methyl methacrylate) in a reaction mixture allows diazocyclopropane to be trapped under the same conditions in 1,3-dipolar cycloaddition, which, along with deuterium exchange data,[12] suggests rapid interconversions of cyclopropyldiazonium ions and diazocyclopropane. In the absence of appropriate scavengers, cyclopropyldiazonium intermediates easily undergo deazotization to give cyclopropyl and allyl esters of the acids employed for activation of alkyl nitrites.

Experimental

^{1}H NMR spectra were recorded on Bruker AC-200 and Bruker AM-300 spectrometers (200 and 300 MHz, respectively) in $CDCl_3$ with 0.05% Me_4Si as the internal standard. Reaction products were isolated by preparative TLC on Merck silica gel 60 (0.040—0.063 mm). Commercial Merck naphthols, malononitrile, acrylates, and cyclopropylamine were used without additional purification. 1-Nitroso-2-naphthol was prepared according to a standard procedure.[7] The physical and spectroscopic characteristics of the compounds obtained correlate with the literature data.[5,6]

Azo coupling of cyclopropyldiazonium with naphthols. A solution of alkyl nitrite (5 mmol) in 5 mL of $CHCl_3$ was added at 5 °C to a stirred solution of 1- or 2-naphthol (3.5 mmol) and cyclopropylamine (5 mmol) in 10 mL of $CHCl_3$. The reaction mixture was kept for 13 to 16 h. Then the solvent and the isoamyl alcohol or *n*-butanol that formed were removed *in vacuo* and the reaction products were isolated by preparative TLC with benzene—Et_2O (5 : 1) as an eluent. 1-(Cyclopropylazo)-2-naphthol (**3**) was obtained from 2-naphthol in ~60% yield, R_f 0.75. In the reactions with 1-naphthol, a mixture of 2-cyclopropylazo- (**4**) and 2,4-di(cyclopropylazo)-1-naphthols (**6**) (molar ratio 1 : 1, R_f 0.85) and 4-cyclopropylazo-1-naphthol (**5**) (R_f 0.75) was isolated (see Ref. 1).

5-(Cyclopropylazo)-8-hydroxyquinoline (9).[5] A solution of isoamyl nitrite (0.58 g, 5 mmol) in 5 mL of $CHCl_3$ was added at 5 °C for 20 min to a stirred mixture of 8-hydroxyquinoline (0.37 g, 2.5 mmol), TFA (6 mg, 0.5 mmol), and cyclopropylamine (0.29 g, 5 mmol) in 10 mL of $CHCl_3$. The reaction mixture was kept at 5 °C for 13 to 16 h. The solvent and the isoamyl alcohol that formed were removed *in vacuo* and the target product was isolated by preparative TLC with MeOH—benzene (1 : 2) as an eluent to give compound **9** (0.11 g, 21%), R_f 0.73.

2-(Cyclopropylhydrazono)malononitrile (10).[6] A solution of cyclopropylamine (0.32 g, 5.6 mmol) in 1 mL of $CHCl_3$ was added at 5 °C to a magnetically stirred solution of malononitrile (0.23 g, 3.5 mmol) in 20 mL of $CHCl_3$. The reaction mixture was kept at 5 °C for 13 to 16 h. Then a solution of isoamyl nitrite (0.66 g, 5.6 mmol) in 2 mL of $CHCl_3$ was added with stirring at the same temperature for 20 min. The mixture was stirred for 2 h and kept at 5 °C for an additional 16 h. The solvent and isoamyl alcohol were removed *in vacuo*. Preparative TLC (Et_2O—benzene, 1 : 3) of the residue gave hydrazone **10** (0.24 g, 52%), R_f 0.80.

Nitrosation of cyclopropylamine in the presence of an equimolar amount of benzoic acid. Benzoic acid (30 mg, 0.25 mmol) was added at 5 °C to a solution of cyclopropylamine (14 mg, 0.25 mmol) and Bu^nONO (25 mg, 0.25 mmol) in 0.4 mL of $CHCl_3$. The reaction mixture was kept for 16 h, whereupon volatile components were removed. Microdistillation of the residue *in vacuo* (10 Torr, bath temperature 80—90 °C) gave a fraction (24 mg, 60%) containing allyl and cyclopropyl benzoates **11a** and **12a** in the molar ratio ~4 : 1, respectively (^{1}H NMR data). ^{1}H chemical shifts for ester **11a** agree with the literature data[13] for $PhCOOCDHCH{=}CH_2$.

Cyclopropyl benzoate (12a). ^{1}H NMR ($CDCl_3$), δ: 0.85 (m, 4 H, CH_2CH_2); 4.35 (m, 1 H, CH); 7.31—7.50 and 8.05—8.20 (m, 5 H, Ph). Earlier,[14] ester **12a** was synthesized by cyclopropanation of vinyl benzoate with CH_2I_2 in the presence of $EtZnOCOCF_3$.

6-Methoxycarbonyl-6-methyl-4,5-diazaspiro[2.4]hept-4-ene (13).[8] A solution of Bu^nONO (0.36 g, 3.5 mmol) in 5 mL of $CHCl_3$ and then cyclopropylamine (0.2 g, 3.5 mmol) in 5 mL of $CHCl_3$ were added at 5 °C for 10 min to a stirred mixture of methyl methacrylate (0.35 g, 3.5 mmol) and PhCOOH (4 mg, 0.35 mmol) in 10 mL of $CHCl_3$. The reaction mixture was kept at 5 °C for 11 days. The solvent and the *n*-butanol that formed were removed *in vacuo*. Distillation of the residue *in vacuo* gave compound **13** (0.36 g, 61%).

Nitrosation of cyclopropylamine in the presence of methyl acrylate. The reaction between methyl acrylate (0.33 g, 3.8 mmol), cyclopropylamine (0.2 g, 3.5 mmol), and isoamyl nitrite (0.41 g, 3.5 mmol) in 25 mL of $CHCl_3$ in the presence of PhCOOH (4 mg, 0.35 mmol) (reaction time 40 h) was carried out according to the above procedure. After the solvent and volatile compounds were removed from the reaction mixture, the residue (0.25 g) contained 6-methoxycarbonyl-4,5-diazaspiro[2.4]hept-5-ene (**14**)[9] and methyl 3-(cyclopropylamino)propionate (**15**)[10] in the molar ratio ~1 : 1.4 (^{1}H NMR data).

Nitrosation of cyclopropylamine in the presence of methyl methacrylate and an equimolar amount of Me_3CCOOH. A mixture of methyl methacrylate (0.175 g, 1.75 mmol), cyclopropylamine (0.10 g, 1.75 mmol), Me_3CCOOH (0.18 g, 1.75 mmol), and *n*-butyl nitrite (0.18 g, 1.75 mmol) in 4 mL of $CHCl_3$ was kept at 5 °C for 16 h. The solvent and the *n*-butanol that formed

were removed *in vacuo*. The nonconsumed pivalic acid was frozen off at −18 °C, and the residue was distilled *in vacuo*. Two main fractions were collected: fraction 1 (0.13 g, b.p. 48—52 °C, 20 Torr) consists of esters **11b** and **12b** (total yield 52%, molar ratio 1.4 : 1); fraction 2 (70 mg (24%), b.p. 89—92 °C, 1 Torr) is pyrazoline **13**.

Allyl pivalate (11b). ^{1}H NMR ($CDCl_3$), δ: 1.20 (s, 9 H, Me_3C); 4.57 (dt, 2 H, CH_2O, ^3J = 5.0 Hz, ^4J = 1.5 Hz); 5.22 and 5.31 (both ddt, 2 H, =CH_2, $^3J_{cis}$ = 10.5 Hz, $^3J_{trans}$ = 17.0 Hz, ^4J = 1.5 Hz); 5.57 (ddt, 1 H, =CH, ^3J = 5.0 Hz, $^3J_{cis}$ = 10.5 Hz, $^3J_{trans}$ = 17.0 Hz).

Cyclopropyl pivalate (12b). ^{1}H NMR ($CDCl_3$), δ: 0.63—0.73 (m, 4 H, CH_2CH_2); 1.12 (s, 9 H, Me_3C); 4.10 (m, 1 H, CH).

Nitrosation of cyclopropylamine with isoamyl nitrite in the presence of 2-naphthol and acrylonitrile (methyl methacrylate). A solution of isoamyl nitrite (0.82 g, 7 mmol) in 5 mL of $CHCl_3$ was added at 5 °C for 20 min to a stirred mixture of 2-naphthol (0.5 g, 3.5 mmol), acrylonitrile (0.19 g, 3.5 mmol) (or methyl methacrylate (0.35 g, 3.5 mmol)), and cyclopropylamine (0.4 g, 7 mmol) in 10 mL of $CHCl_3$. The reaction mixture was kept at 5 °C for 13 to 16 h. The solvent and the isoamyl alcohol that formed were removed *in vacuo*. According to the ^{1}H NMR data, the residue contained compounds **3** and **16** for acrylonitrile as the substrate (ratio ~1 : 1.7) and compounds **3** and **13** for methyl methacrylate (~4 : 1).

This work was financially supported by the Russian Foundation for Basic Research (Project No. 02-03-33365), the President of the Russian Federation (Program for Support of the Leading Scientific Schools, Grant NSh-1987.2003.03), and the Division of Chemistry and Materials Sciences of the Russian Academy of Sciences (Program for Fundamental Investigations "Theoretical and Experimental Study of the Nature of Chemical Bonding and Mechanisms of the Most Important Chemical Reactions and Processes").

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Received January 12, 2004;
in revised form February 9, 2004