Russian Chemical Bulletin, International Edition, Vol. 54, No. 10, pp. 2379—2383, October, 2005

Regioselectivity of reductive debromination of substituted pentabromobenzenes with sodium *tert*-butoxide in DMSO

V. N. Shishkin,[a]* I. V. Tarasova,[a] and K. P. Butin[b]†

[a]N. P. Ogarev Mordovian State University,
68 ul. Bol´shevistskaya, 430000 Saransk, Russian Federation.
E-mail: shishkinvn@mrsu.ru
[b]Department of Chemistry, M. V. Lomonosov Moscow State University,
1 Leninskie Gory, 119992 Moscow, Russian Federation

The regioselectivity of reductive debromination of substituted pentabromobenzenes C_6Br_5X ($X = NH_2$, OMe, Me, H, Cl, F, and NO_2) under the action of Bu^tONa in DMSO containing Bu^tOH has been studied. The reaction followed the halophilic mechanism *via* carbanions.

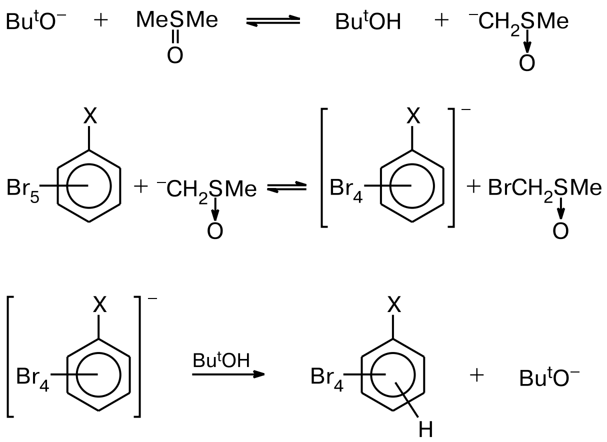
Key words: substituted pentabromobenzenes, reductive debromination, regioselectivity.

In reactions of polybromoarenes with nucleophilic reagents, nucleophilic substitution of bromine is almost always accompanied by reductive debromination (replacement of bromine by hydrogen from a solvent molecule)[1], which makes them different from polyfluorinated and polychlorinated* analogs.

In some cases, reductive debromination can become the major reaction. For instance, reactions of polybromoarenes with sodium alkoxides in acetone,[3,4] ethyl methyl ketone,[3—5] or DMSO[4,6] give exclusively reductive debromination products. This result has been explained[4,6] by the formation of intermediate "soft" bases (namely, enolate anions or a dimsyl anion) upon an acid-base interaction, which serve as effective nucleophiles in these processes; thus, the reaction consists of the transfer of a formally positively charged Br atom from the polybromoarene to the nucleophile to give a carbanion followed by its protonation (heterolytic halophilic[7] mechanism) (Scheme 1).

However, it is worth noting that no convincing proof that the reductive debromination of polybromoarenes follows the heterolytic mechanism has been documented; alternatively, a single-electron transfer mechanism involving radical species can be proposed for these processes (Scheme 2).

Scheme 1



To elucidate in more detail possible mechanisms of the reductive debromination of polybromoarenes, we investigated the effects of the substituents on the regioselectivity of hydrodebromination of some substituted pentabromobenzenes C_6Br_5X ($X = NH_2$, OMe, Me, H, Cl, F, and NO_2) under the action of Bu^tONa in DMSO containing 11% Bu^tOH at 60 °C. The composition of the products was determined by both GLC and ^1H NMR spectroscopy with the use of authentic compounds because isomeric C_6HBr_4X where the H atom is in *meta* and *para* position relative to substituent X are poorly separated by GLC.

With the equimolar ratio of the reagents, all possible isomeric tetrabromo derivatives were observed within the first five minutes of the reaction (Table 1). With an increase in the reaction time, as well as with an excess of Bu^tONa, debromination proceeded farther to give a mixture of tri- and tetrabromo products.

It can be seen in Table 1 that the debromination of pentabromonitrobenzene, pentabromofluorobenzene, and

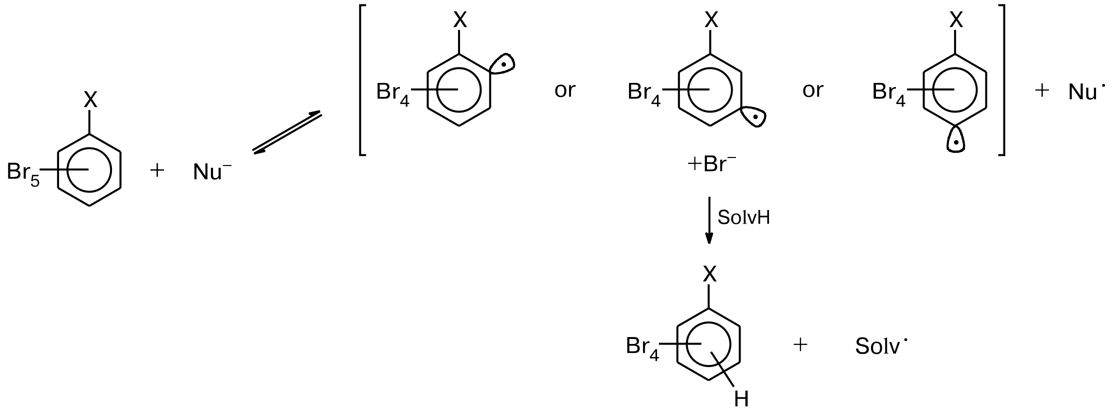
---

† Deceased.

* Only a few examples of reductive dechlorination accompanying nucleophilic substitution in pentachlorobenzonitrile and 2,4,5,6-tetrachloro-1,3-dicyanobenzene in their reactions with amines in DMF and sulfolane (150—250 °C) have been documented.[2]

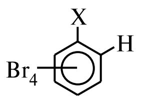
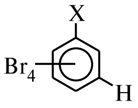
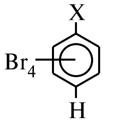
Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 10, pp. 2305—2308, October, 2005.

Scheme 2



SolvH stands for solvent

Table 1. Composition of the reductive debromination products of substituted pentabromobenzenes C_6Br_5X with sodium *tert*-butoxide in DMSO (60 °C)

X	Contents of the products (mol.%)		
			
NO_2	79.9±2.0	12.3±2.7	8.3±1.2
F	44.1±0.8	33.6±0.4	22.2±0.5
Cl	~40	~30	~30
H	5.0±2.0	31.0±2.5	64.0±2.5
Me	6.8±2.0	27.5±2.5	65.7±2.5
OMe	59.3±2.3	23.3±1.7	22.7±1.9
NH_2	15.9±3.0	61.0±3.0	24.0±0.5

Note. The reactions were carried out in the presence of Bu^tOH (11 vol.%). No reductive debromination was observed in Bu^tOH containing Bu^tONa.

pentabromoanisole mainly involves the *ortho*-position relative to the substituent, while pentabromotoluene is debrominated from the *para*-position (pentabromobenzene mainly yields 1,2,4,5-tetrabromobenzene) and pentabromoaniline, from the *meta*-position. The composition of the debromination products from pentabromochlorobenzene was not determined exactly since the ^1H NMR spectrum of the reaction mixture contains overlapping signals for aromatic protons, which are characteristic of both tetrabromochloro- and tribromochlorobenzenes. The signals for the protons of isomeric tetrabromochlorobenzenes have comparable intensities, that for the *ortho*-isomer being slightly dominant.

The regioselectivity of reductive debromination in the case of the halophilic mechanism should be determined by the stability of an intermediate σ-carbanion (see Scheme 1), while the regioselectivity of a reaction involving radical species, by the stability of a polybromoaryl σ-radical (see Scheme 2).

Our experimental data match better the halophilic mechanism. According to this mechanism, bromine (as a formally positively charged species) is abstracted by a nucleophile from the substrate and an intermediate polybromoaryl anion is protonated, since the NO_2, F, and OMe groups better stabilize, due to their $-I$ effects, a σ-carbanion with an anionic center in the *ortho*-position.[8] In the case of pentabromobenzene and pentabromotoluene, the carbanionic center in the *para*-position with respect to the substituent is best stabilized by two electronegative *ortho*-Br atoms. For pentabromoaniline, the aminotetrabromophenyl carbanion in which the carbanionic center and the amino group are *meta* to each other will be most stable.

The heterolytic and radical mechanisms can be distinguished by, *e.g.*, using CH_3OD as a solvent.[9] If the reaction involves an intermediate carbanion, the latter will abstract the deuterium atom from the solvent molecule, while intermediate radical species are stabilized by abstracting hydrogen atom from the methyl group (the methoxide ion is even better donor of $H^\bullet$).[10]

In this context, we carried out debromination of pentabromotoluene with sodium methoxide in a $CH_3OD—CD_3COCD_3$ system (1 : 5). The resulting mixture of tetrabromotoluenes had the same composition (GLC data) as a mixture obtained by debromination with NaOMe in a $MeOH—Me_2CO$ system; however, its ^1H NMR spectrum shows no signals in the regions characteristic of the methyl and aromatic protons. Thus, we obtained tetrabromotoluenes in which the H atoms in the methyl group (because of the increased acidity of pentabromotoluene[11]) and in the aromatic ring are completely replaced by deuterium. The latter suggests that intermediate species in reductive debromination are polybromoaromatic carbanions, *i.e.* the halophilic mechanism is more likely (see Scheme 1).

Experimental

IR spectra were recorded on an InfraLUM FT-02 instrument. ^{1}H NMR spectra were recorded on a Bruker AM 300 instrument (300 MHz).

The purity of the starting and the final compounds was checked by GLC; the purity of all individual products was no less than 97.5—98.5%. GLC analysis was carried out on Chrom-4 and Chrom-42 chromatographs (thermoionic detector; glass columns 3000×3.5 and 1500×3.5 mm, respectively; Chromaton N-AW-HMDS (0.16—0.20 mm) + 5% SE-30 and Chromaton N-Super (0.16—0.20 mm) + 3% OV-17 as stationary phases, respectively; column temperature 200—260 °C; nitrogen as a carrier gas).

Isomeric tetrabromotoluenes,[5] tetrabromoanisoles,[12] 1,2,3,4-tetrabromobenzene,[13] 1,2,4,5-tetrabromobenzene,[14]

Table 2. Yields, melting points, elemental analysis data, and spectroscopic characteristics of the polybromoarenes studied

Compound	Yield (%)	M.p./°C (solvent)	Found/Calculated (%)		Molecular formula	IR (KBr), ν/cm^{-1}	^{1}H NMR, δ (*J*/Hz) [solvent]
			C	H			
3,4,5,6-Tetrabromo-2-chloroaniline	68	238—240 (benzene)	16.42 16.26	0.52 0.45	$C_6H_2Br_4ClN$	3474, 3378 (ν(N—H)), 1590 (δ(N—H))	4.92 (br.s) [CDCl$_3$]
2,3,5,6-Tetrabromo-4-chloroaniline	72	237—238 (benzene)	16.54 16.26	0.65 0.45	$C_6H_2Br_4ClN$	3470, 3371 (ν(N—H)), 1593 (δ(N—H))	5.00 (br.s) [CDCl$_3$]
2,4,6-Tribromo-3-chloroaniline	75	123 (ethanol)	19.63 19.78	0.70 0.83	$C_6H_3Br_3ClN$	3453, 3353 (ν(N—H)), 1595 (δ(N—H))	4.53 (br.s, 2 H, NH$_2$); 7.48 (s, 1 H, H arom.) [CDCl$_3$]
1,2,3,4-Tetrabromo-5-chlorobenzene	72	149 (LP*)	16.69 16.83	0.36 0.24	C_6HBr_4Cl	3088 (ν(Ar—H)), 866 (δ(Ar—H))	8.14 (s) [DMSO-d$_6$]
1,2,4,5-Tetrabromo-3-chlorobenzene	64	217—218 (LP)	16.92 16.83	0.42 0.24	C_6HBr_4Cl	3077 (ν(Ar—H)), 860 (δ(Ar—H))	8.20 (s) [DMSO-d$_6$]
1,2,3,5-Tetrabromo-4-chlorobenzene	89	136 (hexane)	16.75 16.83	0.45 0.24	C_6HBr_4Cl	3084 (ν(Ar—H)), 868 (δ(Ar—H))	8.25 (s) [DMSO-d$_6$]
2,3,5,6-Tetrabromoaniline	49	125 (benzene)	17.91 17.63	0.92 0.74	$C_6H_3Br_4N$	3466, 3379 (ν(N—H)), 1597 (δ(N—H))	5.82 (br.s, 2 H, NH$_2$); 7.37 (s, 1 H, H arom.) [DMSO-d$_6$]
2,3,4,6-Tetrabromoaniline	51	112—113[24] (benzene)	17.75 17.63	0.58 0.74	$C_6H_3Br_4N$	3453, 3379 (ν(N—H)), 1601 (δ(N—H))	5.52 (br.s, 2 H, NH$_2$); 7.72 (s, 1 H, H arom.) [DMSO-d$_6$]
2,3,4,5-Tetrabromoaniline	64	136—137[25] (LP)	17.47 17.63	0.86 0.74	$C_6H_3Br_4N$	3435, 3356 (ν(N—H)), 1589 (δ(N—H))	5.93 (br.s, 2 H, NH$_2$); 7.23 (s, 1 H, H arom.) [DMSO-d$_6$]
1,2,3,5-Tetrabromo-4-nitrobenzene	78	98 (ethanol)	16.31 16.43	0.45 0.23	$C_6HBr_4NO_2$	1541 (ν_{as}(N—O)), 1359 (ν_s(N—O)	8.41 (s) [DMSO-d$_6$]
1,2,4,5-Tetrabromo-3-nitrobenzene	70	155—157 (benzene)	16.62 16.43	0.30 0.23	$C_6HBr_4NO_2$	1545 (ν_{as}(N—O)), 1379 (ν_s(N—O))	8.46 (s) [DMSO-d$_6$]
1,2,3,4-Tetrabromo-5-nitrobenzene	51	75 (benzene)	16.70 16.43	0.33 0.23	$C_6HBr_4NO_2$	1526 (ν_{as}(N—O)), 1341 (ν_s(N—O))	8.50 (s) [DMSO-d$_6$]
2,3,5,6-Tetrabromo-4-fluorobenzoic acid	45	228—230[26] (ethanol—water)	18.25 18.45	0.30 0.22	C_7HBrFO_2	1705 (ν(C=O))	—
2,4,6-Tribromo-3-fluoroaniline	83	98 (ethanol)	20.50 20.72	0.65 0.87	$C_6H_3Br_3FN$	3419, 3300 (ν(N—H)), 1595 (δ(N—H))	4.72 (br.s, 2 H, NH$_2$); 7.57 (d, 1 H, H arom., *J* = 6.6) [CDCl$_3$]
1,2,3,5-Tetrabromo-4-fluorobenzene	51	87 (hexane)	17.31 17.15	0.37 0.24	C_6HBr_4F	3060 (ν(Ar—H)), 855 (δ(Ar—H))	8.24 (d, 1 H, *J* = 7.1) [DMSO-d$_6$]
1,2,4,5-Tetrabromo-3-fluorobenzene	39	126—127 (LP)	17.55 17.15	0.31 0.24	C_6HBr_4F	3065 (ν(Ar—H)), 860 (δ(Ar—H))	7.94 (d, 1 H, *J* = 1.6) [DMSO-d$_6$]

* Light petroleum.

1,2,3,5-tetrabromobenzene,[15] pentabromobenzene,[16] hexabromobenzene,[17] pentabromotoluene,[18] pentabromofluorobenzene,[19] pentabromochlorobenzene,[20] pentabromonitrobenzene,[21] pentabromoaniline,[22] and 2,4,6-tribromo-3-methylaniline[23] were prepared according to described procedures.

1,2,3,4-Tetrabromo-5-chloro- and 1,2,4,5-tetrabromo-3-chlorobenzenes were synthesized by reductive deamination of tetrabromochloroanilines prepared by reduction of the corresponding tetrabromochloronitrobenzenes.[21]

Reduction of tetrabromonitrobenzenes (general procedure). A mixture of the corresponding polybromonitrobenzene (0.022 mol) and reduced iron (15 g, 0.36 mol) in glacial acetic acid (200 mL) was refluxed for 2 h. The reaction mixture was cooled and diluted with water and the precipitate that formed was separated, dried, and recrystallized from benzene.

Deamination of tetrabromochloroanilines was carried out as described for polybromomethoxyanilines.[12] Compounds obtained were purified by column chromatography on L 40/100 silica gel with light petroleum as an eluent (70—100 °C).

1,2,3,5-Tetrabromo-4-chlorobenzene, 1,2,3,5-tetrabromo-4-fluorobenzene, and 1,2,3,5-tetrabromo-4-nitrobenzene were obtained by the Sandmeyer substitution of bromine for the amino group in the corresponding 3-substituted 2,4,6-tribromoanilines as described for polybromomethoxyanilines.[12] The products were additionally purified by column chromatography on Al_2O_3 with hexane as an eluent.

2,4,6-Tribromo-3-chloroaniline, 2,4,6-tribromo-3-fluoroaniline, and 2,4,6-tribromo-3-nitroaniline were obtained by bromination of the corresponding 3-substituted anilines as described for bromination of 3-methylaniline.[23]

1,2,4,5-Tetrabromo-3-nitrobenzene. A mixture of 1,2,4,5-tetrabromobenzene (3.7 g), $NaNO_3$ (1.8 g), and conc. H_2SO_4 (10 mL) was heated on a water bath with stirring for 7 h. The reaction mixture was cooled, poured onto ice, and neutralized with NaOH. The precipitate that formed was filtered off, washed with water, dried, and recrystallized from benzene.

1,2,3,4-Tetrabromo-5-nitrobenzene was obtained by oxidation of 2,3,4,5-tetrabromoaniline.[24] A mixture of 2,3,4,5-tetrabromoaniline (2 g), AcOH (10 mL), 30% H_2O_2 (2.5 mL), and conc. H_2SO_4 (0.2 mL) was heated on a water bath with stirring for 6 h. The reaction mixture was cooled and diluted with water. The precipitate that formed was filtered off, washed with 20% H_2SO_4 and then with water to a neutral reaction, dried, and recrystallized from benzene—light petroleum.

1,2,4,5-Tetrabromo-3-fluorobenzene was obtained by decarboxylation of 2,3,5,6-tetrabromo-4-fluorobenzoic acid prepared as described for pentabromobenzoic acid.[21] A mixture of 2,3,5,6-tetrabromo-4-fluorobenzoic acid (0.5 g) and *N*,*N*-dimethylaniline (20 mL) was heated at 190 °C for 40 min. After cooling, dilute HCl (1 : 1) (50 mL) was added. The precipitate that formed was filtered off, washed with hot 5% Na_2CO_3 and water, dried, and additionally purified by column chromatography on silica gel with light petroleum as an eluent.

The yields, melting points, spectroscopic characteristics, and elemental analysis data for the polybromoarenes obtained are given in Table 2.

Reactions of substituted pentabromobenzenes with Bu^tONa in DMSO (general procedure). A mixture of DMSO (80 mL) and C_6Br_5X (0.002 mol) was kept at constant temperature (60 °C) under flow of argon until the polybromoarene dissolved completely. Then 0.2 *M* Bu^tONa (10 mL) in Bu^tOH was added to the reaction mixture at the above temperature under argon. Samples were withdrawn at intervals from the reaction mixture and treated with 2% HCl; the precipitate that formed was separated, washed to a neutral reaction, dried, and analyzed by GLC and ^1H NMR spectroscopy. The results are given in Table 1.

Debromination of pentabromotoluene with MeONa in $CH_3OD—CD_3COCD_3$. A mixture of pentabromotoluene (80 mg, 0.164 mmol), a solution of NaOMe (2 mL) in CH_3OD (prepared by dissolution of metallic Na in CH_3OD; 0.1 mmol mL^{-1}), and CD_3COCD_3 (10 mL) was heated in a flow of argon under reflux for 0.5 h. The reaction mixture was cooled and concentrated to dryness; the residue was washed with 2% HCl and then with water to a neutral reaction, dried, and analyzed by GLC and ^1H NMR spectroscopy. According to the data from ^1H NMR spectroscopy, a solution of the residue in CCl_4 does not contain even traces of proton-containing compounds. The GLC profile fully agrees with that of a product obtained under analogous conditions in nondeuterated solvents (the degree of conversion of C_6Br_5Me was 90% (GLC); the contents of 2,3,4,5-, 2,3,4,6-, and 2,3,5,6-tetrabromotoluenes in the mixture were 5, 28, and 67%, respectively (^1H NMR)).

References

1. V. N. Shishkin and K. P. Butin, *Izv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim. Nauk*, 1990, 84 [*Izv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim. Nauk*, 1990 (Engl. Transl.)].
2. G. Beck, E. Degener, and H. Heitzer, *Justus Liebigs Ann. Chem.*, 1968, **716**, 47.
3. T. Linden, *Recl Trav. Chim. Pays-Bas*, 1951, **49**, 781.
4. I. Collins and H. Suschitzky, *J. Chem. Soc. C*, 1969, 2337.
5. V. N. Shishkin, K. K. Lapin, B. S. Tanaseichuk, and K. P. Butin, *Zh. Org. Khim.*, 1990, **26**, 2181 [*J. Org. Chem. USSR*, 1990, **26**, 1882 (Engl. Transl.)].
6. J. F. Bunnett and R. R. Victor, *J. Am. Chem. Soc.*, 1968, **90**, 810.
7. N. S. Zefirov, in *Mekhanizmy geteroliticheskikh reaktsii* [*Mechanisms of Heterolytic Reactions*], Nauka, Moscow, 1976, 113 (in Russian); N. S. Zefirov and D. I. Machon´kov, *Chem. Rev.*, 1982, **82**, 615.
8. G. E. Hall, R. Piccolini, and J. D. Roberts, *J. Am. Chem. Soc.*, 1955, **77**, 4540.
9. J. F. Bunnett and C. C. Wamser, *J. Am. Chem. Soc.*, 1967, **89**, 6712.
10. D. A. Evans and D. J. Baillargeon, *Tetrahedron Lett.*, 1978, 3319.
11. K. P. Butin, A. A. Ivkina, V. N. Shishkin, and O. A. Reutov, *Vestn. Mosk. Univ., Ser. 2: Khim.*, 1983, **24**, 382 [*Bull. Moscow Univ., Div. Chem.*, 1983, **24** (Engl. Transl.)].
12. V. N. Shishkin, B. S. Tanaseichuk K. K. Lapin, A. A. Ivkina, and K. P. Butin, *Zh. Org. Khim.*, 1984, **20**, 2588 [*J. Org. Chem. USSR*, 1984, **20**, 2357 (Engl. Transl.)].
13. H. Furujama and S. Fukushi, *J. Synth. Org. Chem. Jpn*, 1971, **29**, 413.

14. W. Qwist and H. Wikman, *Acta Acad. Ab., Math. Phys.*, 1959, 1.
15. M. P. Doyle, M. A. Van Lente, R. Mowat, and W. F. Fobare, *J. Org. Chem.*, 1980, **45**, 2570.
16. H. Furujama and J. Fudzi, *J. Synth. Org. Chem. Jpn*, 1971, **29**, 92.
17. D. J. Berry and B. J. Wakefield, *J. Chem. Soc. C*, 1969, 2342.
18. G. F. Hennion and J. G. Andersen, *J. Am. Chem. Soc.*, 1946, **68**, 424.
19. N. N. Vorozhtsov, G. G. Yakobson, and N. I. Krizhechkovskaya, *Zh. Obshch. Khim.*, 1961, **31**, 1674 [*J. Gen. Chem. USSR*, 1961, **31** (Engl. Transl.)].
20. W. I. Awad and A. I. Hashem, *Egypt. J. Chem.*, 1973, **16**, 269.
21. V. N. Shishkin, I. Yu. Bolusheva, K. K. Lapin, and B. S. Tanaseichuk, *Zh. Org. Khim.*, 1991, **27**, 1486 [*J. Org. Chem. USSR*, 1991, **27**, 1303 (Engl. Transl.)].
22. USSR Inventor´s Certificate 1 606 508; *Byull. Izobret.*, 1990, 42.
23. W. Fuchs, *Monatsh. Chem.*, 1915, **36**, 113.
24. G. A. Kubiczak, F. Oesch, J. T. Borlakoglu, H. Kunz, and L. W. Robertson, *J. Agric. Food Chem.*, 1989, **37**, 1160.
25. C. van de Bunt, *Recl Trav. Chim. Pays-Bas*, 1929, **48**, 121.
26. G. B. Deacon and G. J. Farquharson, *Aust. J. Chem.*, 1976, **29**, 627.

Received April 6, 2004;
in revised form June 25, 2004