Pergamon

Tetrahedron Vol. 50, No. 12, pp. 3797-3802, 1994

0040-4020/94 $6.00+0.00

0040-4020(94)E0099-F

Surfactant Control of the Ortho/Para Ratio in the Bromination of Anilines. 2.

Giorgio Cerichelli, Giovanna Mancini

Centro CNR di Studio sui Meccanismi di Reazione, Dipartimento di Chimica, Università degli Studi di Roma"La Sapienza", P.le A. Moro 2, 00185 Roma (Italy)

Luciana Luchetti

Dipartimento di Scienze e Tecnologie Chimiche, Università degli Studi di Roma "Tor Vergata" Via della Ricerca Scientifica, 00133 Roma (Italy)

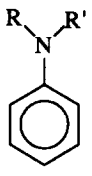
Abstract: We report the bromination of some N,N-disubstituted anilines (N-ethyl-N-methylaniline, N,N-diethylaniline, N-butyl-N-methylaniline, 1-phenylpyrrolidine, 1-phenylpiperidine) both in aqueous suspension of cetyltrimethylammonium tribromide ($CTAB_3$) and in homogeneous solution ($CHCl_3$). In the presence of surfactant we observed a regioselectivity different from that observed in homogeneous conditions. The regioselectivity seems to depend on the nature of the substituents on the nitrogen of the aniline as well as on the temperature. An explanation based on specific interactions between the aniline and the packed structure of the aggregate is proposed.

Introduction

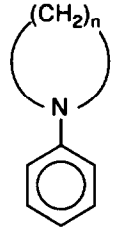
In a previous paper[1] we reported about the bromination reaction of three anilines (aniline, N-methylaniline, N,N-dimethylaniline) in aqueous suspension of cetyltrimethylammonium tribromide ($CTAB_3$). The results showed that the surfactant induced a regioselectivity opposite to that observed in various homogeneous conditions: namely we obtained a good yield in *ortho* product (up to 70%). We attributed this effect to the orientation of the substrate at the aggregate-water interface. In our opinion the orientation depended mostly on the presence of hydrophobic substituents on the nitrogen of the aniline, because we obtained the highest regioselectivity in the bromination of N,N-dimethylaniline. The presence of alkyl substituents on the nitrogen makes hydrophobic the part of the molecule that was hydrophilic and changes the orientation of the aniline at the surface of the aggregate; the new orientation brings the ortho position close to Br_3^-, which as a specific counterion,[2] is located deep in between the head groups of the surfactant. Because the results we obtained were

interesting both *per se*, as a synthetic result, and as a tool for investigating the anisotropy of the aggregate-water interface, it seemed worthwhile to us to investigate further this reaction in order to obtain hopefully a higher regioselectivity and to clarify which factors are responsible for the regioselectivity.

In this paper we report the bromination reaction of a series of anilines (N-ethyl-N-methylaniline **1**, N,N-diethylaniline **2**, N-butyl-N-methylaniline **3**, 1-phenylpyrrolidine **4**, 1-phenylpiperidine **5**) in aqueous suspension of $CTAB_3$. As a reference organic solvent we chose $CHCl_3$ because it favours monobromination. Substrates **1**, **2**, and **3** were chosen with the purpose of forcing the orientation of the amino group toward the inside of the aggregate by increasing the hydrophobicity of substituents; substrates **4** and **5** were chosen with the aim of reducing the steric hindrance on the ortho position relatively to **1**, **2**, and **3** by immobilising the alkyl chains into a ring and of having a different hindrance on the ortho position between **4** and **5**. In **4**, in fact, the pyrrolidinic and aromatic rings are coplanar, whilst in **5** the two rings do not lie on the same plane.[3]



1 $R=CH_3$, $R'=CH_2CH_3$
2 $R,R'=CH_2CH_3$
3 $R=CH_3$, $R'=(CH_2)_3CH_3$



4 n=4
5 n=5

Experimental

CTAB (Fluka) was purified by the procedure of Duynstee and Grundwald.[4]
N,N-Diethylaniline (Fluka) of the highest purity was used without further purification.
The NMR spectra were recorded on a Varian XL 300 spectrometer, in $CDCl_3$ as a solvent and chemical shifts are reported in ppm donfield from TMS.

$CTAB_3$. 80 mg (0.5 mmoles) of bromine were added under mild stirring to 10 mL of a 0.05 M aqueous solution of CTAB. The addition of bromine yielded an amorphous yellow precipitate ($CTAB_3$). The same heterogeneous solution was heated for obtaining an orange clear solution which on cooling to room temperature yielded a yellow crystalline precipitate. Filtration yielded 254 mg (97%) of $CTAB_3$.

Both the amorphe and the crystalline precipitate were characterized by elemental analysis. Analysis Calcd for $C_{19}H_{42}NBr_3$: H 8.07, C 43.53, N 2.67, Br 45.72; Found: H 8.13, C 43.42, N 2.70, Br 45.75.

N,N-dialkylanilines. We modified the procedure reported by Bent et al.[5]: 0.187 moles of N-methylaniline (Fluka) and 0.187 moles of the alkyl bromide (Fluka) were added to 200 mL of benzene. After three days at room

temperature the precipitate was filtered and washed with Et_2O. The filtrate was dissolved in aqueous solution of Na_2CO_3 and the aqueous solution was extracted with Et_2O. The organic layer was dried over Na_2SO_4. Removal of solvent by rotary evaporation yielded the product (80%) which was characterized by ^1H NMR and ^{13}C NMR.

N-Ethyl-N-methylaniline. ^1H NMR: δ=1.190 (t, 3H); δ=2.969 (q, 2H); δ=3.456 (s, 3H); δ=6.782 (m, 3H); δ=7.304 (m, 2H). ^{13}C NMR: δ=11.20; δ=37.45; δ=46.82; δ=112.42; δ=116.06; δ=129.17; δ=149.13.

N-Butyl-N-methylaniline. ^1H NMR[6]: δ=1.010 (t, 3H); δ=1.390 (m, 2H); δ=1.600 (m, 2H); δ=2.961 (s, 3H); δ=3.348 (t, 2H); δ=6.729 (m, 3H); δ=7.265 (m, 2H). ^{13}C NMR: δ=14.02, δ=20.36, δ=28.81, δ=38.23, δ=52.48, δ=112.02, δ=115.73, δ=129.08, δ=149.32.

1-Phenylazacycloalkanes were prepared by standard procedures.[3, 7]

Product Standards

Preparation of 4-bromo-N,N-dialkylanilines. 1.5 mmoles of N,N-dialkylaniline were added under stirring to 30 mL of $CHCl_3$ 0.05 M in bromine. After decoloration the reaction mixture was washed with aqueous 0.1 M Na_2CO_3 solution and dried over Na_2SO_4. Removal of solvent by rotary evaporation yielded the product which was characterized by ^1H NMR and ^{13}C NMR.

4-Bromo-N-ethyl-N-methylaniline. ^1H NMR: δ=1.126 (t, 3H), δ=2.894 (s, 3H), δ=3.386 (q, 2H), δ=6.593 (d, 2H), δ=7.310 (d, 2H). ^{13}C NMR: δ=11.09, δ=37.56; δ=46.90, δ=107.88, δ=114.00, δ=131.81, δ=148.05.

4-Bromo-N,N-diethylaniline. ^1H NMR[8]: δ=1.169 (t, 3H); δ=3.340 (q, 2H); δ=6.565 (d, 1H); δ=7,293 (d, 2H). ^{13}C NMR: δ=12.39, δ=44.44, δ=106.94, δ=113.39, δ=131.83, δ=146.68.

4-Bromo-N-butyl-N-methylaniline.^1H NMR; δ=1.003, (t, 3H); δ=1.399, (m, 2H); δ=1.589, (pent., 2H); δ=2.938, (s, 3H); δ=3.339, (t, 3H); δ=6.595, (d, 2H); δ=7.331, (d, 2H). ^{13}C NMR: δ=13.98, δ=20.29, δ=28.65, δ=38.31, δ=52.48, δ=107.49, δ=113.56, δ=131.67, δ=148.21.

1-(4-Bromophenyl)pyrrolidine. ^1H NMR: δ=2.012 (m, 4H); δ=3.241 (m, 4H); δ=6.430 (d, 2H), δ=7.286 (d, 2H). ^{13}C NMR: δ=25.44, δ=47.69, δ=107.13, δ=113.20, δ=131.64, δ=146.76.

1-(4-Bromophenyl)piperidine.^1H NMR: δ=1.544, (pent., 1H); δ=1.749 (pent, 2H); δ=3.142, (t, 2H); δ=7.042, (d, 2H); δ=7.281, (d, 2H). ^{13}C NMR: δ=22.92, δ=24.49, δ=52.12, δ=114.20, δ=119.29, δ=131.81, δ=147.92.

Bromination reaction in the presence of $CTAB_3$

10 mL of the aqueous suspension (0.05 M) of $CTAB_3$ were thermally equilibrated to the desired temperature (0°, 10° or 25° C) before adding 0.5 mmoles of aniline. After decoloration the reaction mixture was extracted with Et_2O, avoiding hard shaking in order to prevent emulsion formation. The organic fraction was washed with an aqueous saturated solution of $NaHCO_3$, then concentrated and analyzed by GC-MS. Yields

reported in Table 1 were averaged over three experiments and over three injection for each experiment. Results were in agreement within 1.5%.

Both the amorphe and the crystalline precipitate were used, the first yielded 80% of monobrominated product, while the second one yielded 90% of monobrominated product (these yields apply to each of the substrates). Yields in ortho product, normalized with respect to monobrominated product were the same for the two procedures.

Bromination reaction in $CHCl_3$

0.5 mmoles of N,N-dialkylaniline were added under stirring to 50 ml of $CHCl_3$ 0.01 M in bromine both at 0° and 25° C. After decoloration the reaction mixture was washed with an aqueous saturated solution of $NaHCO_3$, then concentrated and analyzed by GC-MS. Yields reported in Table 2 were averaged over three experiments and over three injections for each experiment. Results were in agreement within 1.5%.

Results

We carried out the bromination reaction of anilines **1**-**5** in aqueous suspension of $CTAB_3$ at 0° C and 25° C and of anilines **1** and **4** at 10° C. It must be pointed out that the reaction was always carried out in the presence of a precipitate (cetyltrimethylammonium tribromide). The results, summarized in Table 2, indicate that the bromination reaction of the anilines proceeded with a regioselectivity which seems to depend on the temperature as well as on the structure of the aniline. As a reference we have carried out the bromination reaction in homogeneous conditions in $CHCl_3$ at 0° C and 25° C for all the anilines. Results are summarised in Table 2.

Table 1. Product Distribution[a] for the Bromination Reaction of Anilines in Aqueous $CTAB_3$.

	0° C		25° C		10° C	
aniline	*%ortho*	*%para*	*%ortho*	*%para*	*%ortho*	*%para*
N,N-dimethylaniline[b]	70	30	2	98		
N-ethyl-N-methylaniline	50	50	2	98	2	98
N,N-diethylaniline	50	50	2	98		
N-butyl-N-methylaniline	50	50	2	98		
1-phenylpyrrolidine	85	15	2	98	2	98
1-phenylpiperidine	20	80	2	98		

a Yields are normalized with respect to monobrominated products.
b Reference 1

Table 2. Product Distribution[a] for the Bromination Reaction of Anilines in $CHCl_3$.

	0° C		25° C	
aniline	*%ortho*	*%para*	*%ortho*	*%para*
N,N-dimethylaniline[b]	-	100	2	98
N-ethyl-N-methylaniline	-	100	2	98
N,N-diethylaniline	-	100	2	98
N-butyl-N-methylaniline	-	100	2	98
1-phenylpyrrolidine	-	100	2	98
1-phenylpiperidine	-	100	2	98

a Yields are normalized with respect to monobrominated products.
b Reference 1

Discussion

Results of the experiment carried out at 25° C in aqueous suspension of $CTAB_3$ (Table 1) showed the regioselectivity usually expected for the bromination reaction (see results of bromination reaction in $CHCl_3$ reported in Table 2). A completely different regioselectivity was observed in aqueous $CTAB_3$ at 0° C (Table 1). We carried out the experiment at 10° C to clarify the dependence of the surfactant induced regioselectivity on the temperature. Results of this experiment, no difference with respect to the reaction carried out at 25° C (Table 1), demonstrate that the presence of the surfactant does not simply modify the activation energy for the formation of the two isomers. Variations in the product distribution between 0° and 10° C are in fact so large that they cannot be explained on the basis of different activation energies.

If we observe the trend of the distribution product at low temperature in aqueous $CTAB_3$, results relative to aniline **1**, **2** and **3** show that the higher hydrophobicity of the amino group with respect to N,N-dimethylaniline lowers the yield in *ortho* isomer. Two hypotheses could explain these results. The first one is that the ortho position is hindered by nitrogen substituents bigger than methyl groups. The second one ascribes to the increased hindrance of the amino group the impossibility of penetrating the packed structure of the aggregate with the orientation which favors bromination of the ortho position. Results concerning anilines **4** and **5** seem to favor this second hypothesis. In fact the hindrance on the ortho position is lower[3] for **5** than for **4**, whilst hydrophobicity of amino group is higher for **5** than for **4**. The combination of hydrophobicity of the amino group and of a low hindrance on the ortho position should favour, according to the first hypothesis, bromination of the ortho position for **5** rather than for **4**. Because we obtained a higher yield of ortho product in the bromination of **4**, we believe that the coplanarity of the heterocyclic and of the aromatic rings, even if hinders the ortho position comparedwith **5**, allows a good fit of the aniline in a narrow groove of the aggregate. The geometry of aniline **5** in which the two rings do not lie on the same plane disfavors penetration of the molecule into the aggregate with respect to **4**.

In our hypothesis the geometry and consequently the location of the aniline have a fundamental role, but our hypothesis does not explain the role of temperature. We mostly believe that at 0° C there should be a highly favourable interaction between the aggregate and the aniline due to the packing of the aggregate, the tight interaction would keep the ortho position close to the brominating agent. At higher temperatures thermal shaking makes the interaction less specifically oriented. A result that indeed reinforces this hypothesis is the fact that the yield in monobrominated product is >90% if the reaction is carried out in the presence of a crystalline precipitate, and is 80% if the reaction is carried out in the presence of amorfe precipitate. This result seems to demonstrate that the crystalline packing allows a tighter interaction between the aggregate and the aniline, which slows down the diffusion of the monobrominated product in the aggregate. It could be argued that at 0° C the reaction takes place at the solid-water interphase whilst at 25° C it takes place at the micelle-water interphase, but we found out that filtration of precipitate (preparation of $CTAB_3$, Experimental), at room temperature is quantitative (97%); this fact makes us sure that even at 25° C the solution does not contain any $CTAB_3$ micellar aggregate.

Summary

On the basis of the results we obtained in the bromination reaction of **1**, **2** **3** and **5** in the presence of $CTAB_3$, it could be argued either that the orientation of the amino group of these anilines is mostly toward the water phase as compared to **4** or that, most probably, they are localised in larger grooves where the interaction with the aggregate and the brominating agent is looser. It seems evident that both hydrophobicity of the amino group and a tight interaction with the aggregate should be necessary to bring the ortho position close to the brominating agent.

References

1. Cerichelli, G.; Luchetti, L.; Mancini G. *Tetrahedron Lett.*, **1989**,*30*, 6209-6210.
2. a) Cerichelli, G.; Grande,.C.; Luchetti, L.; Mancini, G. *J. Org. Chem.* **1991**, *56*, 3025-3030; b) Bunton, C. A. In *Cationic Surfactants: Physical Chemistry* ; Rubingh D. N., Holland P. M. Eds., p 323. Marcel Dekker, Inc.: New York, 1991.
3. Cauletti, C.; Cerichelli, G; Grandinetti, F.; Luchetti, L.; Speranza, M. *J. Phys. Chem.*, **1988**, *92*, 2751-2753.
4. Duynstee, E. F. J.; Grunwald E. *J. Am. Chem. Soc.* **1959**, *81*, 4540-4542.
5. Bent, R. L.; Dessloch, J. C.; Duennebier, F. C.; Fasset, D. W.; Glass, D. B.; James, T. H.; Julian, D. B.; Ruby, W. R.; Snell, J. M.; Sterner, J. H.; Thirtle, J. R.; Vittum, P. W.; Weissberger, A. *J. Am. Chem. Soc.* **1951**, *73*, 3100-3125.
6. Paukstelis, J. V.; Kim, M. *J. Org. Chem.* **1974**, *39*, 1494-1499.
7. a) Bird, B.; Knipe, A. C.; Stirling, C. J. M. S. *J. Chem. Soc., Perkin Trans. 2* , **1973**, 1215-1220. b) Horning, C.; Bergstrom, F. W. *J. Am. Chem. Soc.* **1945**, *67*, 2110-2111. c) Heine, H. W.; Kapur, B. L.; Mitch, C. S. *J. Am. Chem. Soc.* **1954**, *76*, 1173.
8. Koleva, V.; Galabov, B; Simov, D. *Org. Magn. Reson.* **1978**, *11*, 475-477

(*Received in UK* 20 *September* 1993; *revised* 17 *January* 1994; *accepted* 21 *January* 1994)