Pergamon

Tetrahedron, Vol. 52, No. 7, pp. 2465-2470, 1996
Copyright © 1996 Elsevier Science Ltd
Printed in Great Britain. All rights reserved
0040-4020/96 $15.00 + 0.00

0040-4020(95)01067-X

Surfactant Control of the Ortho/Para Ratio in the Bromination of Anilines. 3

Giorgio Cerichelli*

Dipartimento di Chimica, Ingegneria Chimica e Materiali, Università dell'Aquila, Via Vetoio 67010, L'Aquila, Coppito Due, (Italy)

Luciana Luchetti

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

Giovanna Mancini*

Centro CNR di Studio sui Meccanismi di Reazione, Dipartimento di Chimica, Università degli Studi di Roma "La Sapienza",
P.le A. Moro 5, 00185 Roma (Italy)

Abstract: We report the bromination of N,N-dimethylaniline in aqueous suspension of cetylpyridinium tribromide, cetylquinuclidinium tribromide, laurylquinuclidinium tribromide, cetyltributylammonium tribromide, cetyldimethyl-2-hydroxyethylammonium tribromide, 1,2-bis(cetyl-N,N-dimethylammonium)ethane tribromide, 1,3-bis(cetyl-N,N-dimethylammonium)propane tribromide, 1,4-bis(cetyl-N,N-dimethylammonium)butane tribromide, (2S,3S)-2,3-dimethoxy-1,4-bis(N-cetyl-N,N-dimethylammonium)butane tribromide. The nature of the head groups of the surfactant, as well as the length of the hydrophobic chain, influence the regioselectivity of the reaction and permits a hypothesis on the structure of the aggregates.

INTRODUCTION

In connection with our interest in surfactant controlled regioselective reactions,[1] we have recently[1d] reported about the bromination reaction of some N,N-disubstituted anilines carried out in aqueous suspension of cetyltrimethylammonium tribromide (CTAB$_3$) at 0 °C. Under those conditions the reaction undergoes with a regioselectivity which, for some of the anilines we took into consideration, yields mostly the *ortho* bromo product (up to 85%) whereas the *para* product is usually the predominant one.[1d, 2] Our hypothesis ascribed the regioselectivity we observed in aqueous CTAB$_3$ at low temperature, to the specific interaction between the structure of the aniline and that of the surfactant aggregate. Hydrophobicity of the substituents on the nitrogen of the aniline was shown to play a fundamental role on the fitting of the aniline with the aggregate. It seemed then worthwhile to investigate which role is played by the structure of the surfactant. In this paper we report the bromination of N,N-dimethylaniline in aqueous suspension of cetylpyridinium tribromide **1**, cetylquinuclidinium tribromide **2**, laurylquinuclidinium tribromide **3**, cetyltributilammonium tribromide **4**, cetyldimethyl-2-hydroxyethylammonium tribromide **5**, 1,2-bis(cetyl-N,N-dimethylammonium)ethane tribromide **6**, 1,3-bis(cetyl-N,N-dimethylammonium)propane tribromide **7**, 1,4-bis(cetyl-N,N-dimethylammonium)butane tribromide **8**, (2S,3S)-2,3-dimethoxy-1,4-bis(N-cetyl-N,N-dimethylammonium)butane tribromide **9**. N,N-dimethylaniline was chosen because showed a high regioselectivity in the bromination reaction carried out in aqueous $CTAB_3$.[1d]

DISCUSSION

In Table we summarize the results obtained in the bromination reaction of N,N-dimethylaniline in aqueous suspension of tribromide salts at 0° and 25° C and we compare them with the results previously obtained in the reaction carried out in aqueous $CTAB_3$.[1b]

Table. Product Distribution[a] for the Bromination Reaction of N,N-Dimethylaniline in Aqueous Suspension of Various Surfactants.

	0° C		25° C	
Surfactant	% *ortho*	% *para*	% *ortho*	% *para*
1	85	15	2	98
2	70	30	2	98
3	35	65	2	98
4	30	70	-	100
5	-	100	-	100
6	-	100	-	100
7	-	100	-	100
8	-	100	-	100
9	50	50	2	98
$CTAB_3$[b]	70	30	2	98

[a] All yields are normalized with respect to monobrominated products

[b] Reference 1d

While the experiments carried out at 25° C in aqueous suspension of tribromide salts showed the regioselectivity expected for this reaction under homogeneous[1d,2] conditions (*i. e.* the formation of the *para* isomer), the reaction carried out at 0° C undergoes with a regioselectivity which depends strongly on the structure of the cationic head group and on the chain length. As we have already emphasised[1d] the role of temperature in this experiment, our discussion will concern the structure of the surfactants.

Small variations in the stucture of the cationic head group as compared with $CTAB_3$, have small effects on the regioselectivity of the bromination reaction. In fact, the bromination reaction carried out in aqueous $CTAB_3$[1b] or **1** or **2** showed a similar regioselectivity. Our hypothesis ascribed the regioselectivity observed in aqueous $CTAB_3$ to grooves on the surface of the aggregate sized to accommodate some anilines better than others. Small variations in the structure of the head group should not modify deeply these grooves and, consequently, they do not modify strongly the product distribution obtained in aqueous **1** or **2** with respect to the bromination reaction carried out in aqueous $CTAB_3$. The tighter structure of the aggregate due to the aromatic ring of pyridinium and the stacked interactions between the head groups of the surfactant and the aromatic ring of the aniline should be responsible for the small increase of *ortho* product yielded by the reaction carried out in aqueous suspension of **1**. The quinuclidinium was a rigid structure with a steric hindrance very similar to that of the trimethylammonium ion and, consequently, we did not observe any variation in the product distribution with respect to the reaction carried out in $CTAB_3$. In the study of other reactions (decarboxylations[3] cyclizations[4]) the aggregates formed by tetradecylquinuclidinium bromide showed a behaviour similar to that of cetyltrimethylammonium bromide (CTAB). Is is true that under the conditions in which we carried out our investigation, we did actually deal with a heterogeneous aggregate, while the above mentioned investigations[3-4] concerned micellar aggregates, but it is reasonable to assume that the surface of a micellar aggregate would be similar to that of a heterogeneous aggregate.

The increase of the steric hindrance of the head groups yielded an inversion of the trend observed in the presence of **1**, **2** and $CTAB_3$, in fact the bromination reaction carried out in aqueous suspension of **4** at 0° C yielded *p*-bromo-N,N-dimethylaniline as the major product. It has been reported[3e-5] that the surface of cetyltetrabutylammonium bromide micellar aggregates has a minor content of water with respect to the surfaces of aggregates formed by CTAB. We believe that this could depend, at least partially, on the steric hindrance and on the mobility of butyl groups which fill the grooves on the surface of the aggregates and reduce their size. The structure of the surface of the aggregates is consequently more similar to that of a homogeneous medium.

The substitution of a methyl group (CTAB) with a hydroxyethyl group (cetyldimethyl-2-hydroxyethylammonium bromide) is a small structural variation which scarcely influenced the rate of a cyclization reaction;[6] in contrast it had a considerable effect on the regioselectivity of the bromination reaction, compared with $CTAB_3$. Using an aqueous suspension of **5**, we obtained only the *para* product: the same result expected in homogeneous solution[2] and observed at 25 °C. Our hypothesis to explain such a result is that the hydroxylic group (which is more acidic than water) hydrogen bonds with the aniline (Figure 1) and, as a consequence, the orientation of the aniline at the surface of the aggregate changes. As far as $CTAB_3$[1b] was concerned, we suggested that the amino group was oriented toward the aggregate, because with this orientation the *ortho* position was close to the tribromide anion; with **5** the amino group should be oriented toward the bulk, thereby keeping the *para* position close to the brominating agent.

A notable difference in the regioselectivity is observed with C_{12} alkyl chain surfactant. In this case we obtained a lower yield of *ortho* product using **3** instead of **2**. We believe this result is due to a looser structure and, consequently, an increased content of water on the aggregates formed by shorten chain surfactants. We have previously reported[5c] that, with the same cation head group, a shorther hydrophobic chain increased the content of water on the aggregate surface. We believe that, in the bromination reaction carried out at 0° C in aqueous suspension of **3**, looser and less specific grooves (due to the major content of water) are responsible for the inversion of the trend with respect to **2**.

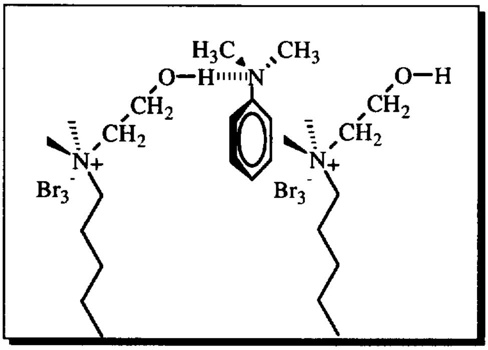

Figure 1

The other surfactants (**6**, **7**, **8**, **9**) can be considered like derivatives of CTAB, with two cetyldimethylamino groups bond by an alkyl chain. The link between the two head groups reduces the head group area and modifies the packing of the aggregate and the structure and size of possible grooves on the surface. The structural changes must be relevant, as we obtained only the *p*-bromoaniline. A large difference in the product distribution is obtained using **9** instead of **8**. The surface of the aggregates formed by this surfactant should allow some penetration, or a different orientation, of the aniline, as we obtained 50% yield of *ortho* product. The two methoxy groups should be responsible of the formation of grooves on the surface of the aggregate, both because of their steric hindrance and of the coordination of water molecules. Using ^{1}H MNR and dynamic laser light scattering investigations, we have evidence[7] that 1,4-bis(cetyl-N,N-dimethylammonium)butane bromide and (2S,3S)-2,3-dimethoxy-1,4-bis(N-cetyl-N,N-dimethylammonium)butane bromide yield aggregates of largely different size.

CONCLUSIONS

The use of different surfactants in the bromination of anilines at low temperature yields a regioselectivity which depends strongly on the structure of the surfactant as well as on that of the aniline.[1d] The reaction can be used as a tool for investigating the structure of the aggregates obtained under the above described conditions. Moreover under the proper condition it can be of synthetic interest.

EXPERIMENTAL

Cetylpyridinium bromide **1** (Fluka) was purified by the procedure of Duynstee and Grundwald.[8] N,N-Dimethylaniline (Fluka) of the highest purity was used without further purification, after checking its purity. 4-Bromo-N,N-dimethylaniline was prepared as previously described.[1d] The ammonium bromides corresponding to the ammonium tribromides **2-8** were prepared as previously described.[3]

Preparation of (2S,3S)-2,3-dimethoxy-1,4-bis(N-cetyl-N,N-dimethylammonium)butane bromide

(2S,3S)-2,3-Dimethoxy-1,4-bis(dimethylamino)butane (10 g, 49 mmol) (Janssen) and 1-bromohexadecane (30 g, 98 mmol) in isopropanol (120 mL) were refluxed for 70 h. After cooling, addition of of Et_2O (200 mL) yielded a white precipitate. The precipitate was collected and washed with Et_2O. Crystalization from $MeOH/Et_2O$ yielded the desired product (37 g, 92%).

Anal. Calcd for $C_{42}H_{90}Br_2N_2O_2$: H 11.16, C 62.03, N 3.45, O 3.94, Br 19.43; Found: H 11.20, C 62.01, N 3.48, O 4.00, Br 19.31.

Preparation of tribromide salts

The same procedure that was used previously for the preparation of $CTAB_3$[1d] was followed. Filtration of the precipitate at 25 °C was quantitative (≥97%). As far as **4** was concerned, a red oil was obtained and was separated from the aqueous phase.

1, Anal. Calcd for $C_{21}H_{38}Br_3N$: H 7.04, C 46.34, N 2.57, Br.44.04; Found: H 7.10, C 46.40, N 2.53, Br 43.97. **2**, Anal. Calcd for $C_{23}H_{46}Br_3N$: H 8.04, C 47.93, N 2.43, Br 41.59; Found: H 8.08, C 47.89, N 2.40, Br 41.62. **3**, Anal. Calcd for $C_{19}H_{38}Br_3N$: H 7.36, C 43.87, N 2.69, Br 46.08;Found: H 7.41, C 43.80, N 2.73, Br 46.06. **4**, Anal. Calcd for $C_{28}H_{60}Br_3N$: H 9.30, C 51.70, N 2.15, Br 36.85; Found: H 9.37, C 51.65, N 2.12, Br 36.86. **5**, Anal. Calcd for $C_{20}H_{44}Br_3NO$: H 8.00, C 43.34 N 2.53, O 2.89, Br 43.25; Found: H 7.98,C 43.31, N 2.50,O 2.90, Br 43.31. **6**, Anal. Calcd for $C_{38}H_{82}Br_6N_2$: H 7.90, C 43.61, N 2.68, Br 45.81; Found: H 7.95, C 43.59,N 2.70, Br 43.76. **7**, Anal. Calcd for $C_{39}H_{84}Br_6N_2$: H 7.98, C 44.17, N 2.64, H 45.21; Found: H 8.01, C 44.13, N 2.60, Br 45.26. **8**, Anal. Calcd for $C_{40}H_{86}Br_6N_2$: H 8.07, C 44.71, N 2.61, Br 44.62; Found: H 8.00, C 44.70, N 2.65, Br 44.65. **9**, Anal. Calcd for $C_{42}H_{90}Br_6N_2O_2$: H 8.00, C 44.46, N 2.47, O 2.86, Br 42.25; Found: H 8.03, C 44.40, N 2.50, O 2.87, Br 42.2.

Bromination reaction in the presence of tribromide salts

We used conditions as those we used in aqueous suspension of $CTAB_3$[1d]. The aqueous suspension of tribromide salt (10 mL, 0.05 M; 0.03 M as far as **2** was concerned) was thermally equilibrated to the desired temperature (0° or 25° C) before adding the aniline (0.5 mmoles; 0.3 mmoles as far as **2** was concerned). After decoloration the reaction mixture was extracted with Et_2O, avoiding hard shaking in order to prevent the formation of an emulsion. The organic fraction was washed with an aqueous saturated solution of $NaHCO_3$, then concentrated and analyzed by GC. Yields reported in Table were averaged over three experiments and over three injections for each experiment. Results were in agreement within 1.5%. Yields of monobrominated products were always >90% with the exception of the reaction carried out in aqueous suspension of **4**, which yielded only 70% of monobrominated products.

ACKNOWLEDGMENTS

For elemental analysis we thank Dr. Luca Antonio Petrilli and Mr. Franco Dianetti of the Servizio di Microanalisi, Area della Ricerca del CNR, Montelibretti (Roma).

Support of this work by CNR Progetto Strategico Beni Culturali, and the MURST is gratefully aknowledged.

REFERENCES

1. (a) Bianchi, M. T.; Cerichelli, G.; Mancini, G.; Marinelli, F. *Tetrahedron Lett.*, **1984**, *25*, 5205-5208; (b) Cerichelli, G.; Luchetti, L.; Mancini G. *Tetrahedron Lett.*, **1989**,*30*, 6209-6210; (c) Cerichelli, G.; Grande,.C.; Luchetti, L.; Mancini, G. *J. Org. Chem.* **1991**, *56*, 3025-3030; (d) Cerichelli, G.; Luchetti, L.; Mancini, G. *Tetrahedron* , **1994**, *50*, 3797-3802.
2. Streitwieser, A. jr.; Heathcock, C. H. Introduction to Organic Chemistry, Macmillan Publishing Co., Inc., 1976, chapt. 32.
3. (a) Bunton, C. A.; Ionescu, L. G. *J. Am. Chem. Soc.* **1973**, *95*, 2912-2917; (b) Bunton, C. A.; Minch, M. J.; Hildago, J.;Sepulveda, L. *J. Am. Chem. Soc.* **1973**, *95*, 3262-3272; (c) Bunton, C. A.; Kanego, A.; Minch, M. J.; Wright, J. L. *J. Org. Chem.* **1975**, *40*, 1321-1324; (d) Germani, R.; Ponti, P. P.; Savelli, G.; Spreti, N.; Bunton, C. A.; Moffat, J. R. *J. Chem. Soc., Perkin Trans. 2* **1989**, 401-405; (e) Germani, R.; Ponti, P. P.; Romeo, T.; Savelli, G.; Spreti, N.; Cerichelli, G.; Luchetti, L.; Mancini, G.; Bunton, C. A. *J. Phys. Org. Chem.* **1989**, *2*, 553-558; (f) Cerichelli, G.; Luchetti, L.; Mancini, G.; Muzzioli, M. N.; Germani, R.; Ponti, P. P.; Spreti, N.; Savelli, G.; Bunton, C. A. *J. Chem. Soc., Perkin Trans. 2* **1989**, 1081-1085.
4. Cerichelli, G.; Mancini, G.; Luchetti, L.; Savelli, G.; Bunton, C. A. *J. Phys. Org. Chem.* **1991**, *4*, 71-76.
5. (a) Bacaloglu, R.; Bunton, C. A.; Cerichelli, G.; Ortega, F. *J. Phys. Chem.*, **1989**, *93*, 1490-1496; (b) Bacaloglu, R.; Bunton, C. A.; Ortega, F. *J. Phys. Chem.*, **1989**, *93*, 1497-1503; (c) Cerichelli, G.; Luchetti, L.; Mancini, G.; Savelli, G.; Bunton, C. A. *J. Coll. Inter. Sci.* **1993**, *160*, 85-92; (d) Cerichelli, G.; Luchetti, L.; Mancini, G.; Savelli, G.; Bunton, C. A. *Langmuir* **1994**, *10*, 3982-3987.
6. Cerichelli, G.; Luchetti, L.; Mancini, G.; Savelli *Tetrahedron* **1995**, *51*, 10281-10288.
7. Mancini, G. Ph. D. Thesis **1988**, Università "La Sapienza", Rome, Italy.
8. Duynstee, E. F. J.; Grunwald E. *J. Am. Chem. Soc.* **1959**, *81*, 4540-4542.

(*Received in UK* 13 *October* 1995; *revised* 6 *December* 1995; *accepted* 7 *December* 1995)