Triple-Branched Cyanine Dyes

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Dale, J. and Eriksen, O. I., 1988. Triple-Branched Cyanine Dyes. – Acta Chem. Scand., Ser. B 42: 242–246.

Y-shaped cyanines having exclusively dimethylamino end groups were synthesized by controlled Vilsmeier-type reaction of linear cyanines with *N,N*-dimethylformamide or 3-dimethylaminoacrolein. The observed mono-substitution and regioselectivity is explained on the basis that attack on the 2-positions of cyanines is sterically hindered by *N*-methyl groups.

The simplest triple-branched cyanine dyes are homologues of the hexamethylguanidinium ion (**1**) such as the monocation **3** and the dications **2** and **4** (Fig. 1). These have a constitutional symmetry that is particularly suited for dynamic NMR studies of conformational symmetry and for the determination of rotational barriers in the bonds of the unsaturated system. Conformational equilibria, if any, can also be studied. Such information is indispensable for a meaningful interpretation of electronic absorption spectra of these simple model chromophores.

Reichardt and coworkers[1-3] have already synthesized several related triple-branched cyanine dyes in which the terminal CN bonds of the chromophoric system form part of various bicyclic aromatic structures. These are obviously not well suited for dynamic NMR studies of exchange processes since they have unsymmetric end-group structures. Thus, no rotational barrier within a given symmetric conformer can in principle be determined. Furthermore, the conjugation of the central cyanine chromophore with the aromatic end groups would render the electronic absorption spectra too complex for theoretical interpretation.

In the simpler series of compounds carrying exclusively dimethylamino end groups, the two first members, **1** and **2**, are known compounds.[4,5] We have previously reported[6] conformational studies of the second member, the tris(dimethylimoniomethyl)methide dication (**2**) (as its diperchlorate), both in solution and in crystalline form. We now report the syntheses of the hitherto unknown tris-(2-dimethylaminoethenyl) methinium mono-cation (**3**) and tris(3-dimethylimonio-1-propenyl)methide dication (**4**), as well as of the less symmetric representative, bis(3-dimethylimonio-1-propenyl)dimethylimoniomethylmethide dication (**9**). A novel preparation of the tris(dimethylamino)methinium cation (**1**) is also described.

Synthetic approaches

We initially tried to adapt the methods used by

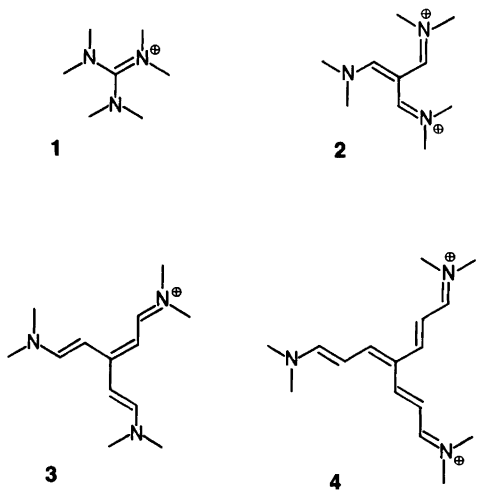

Fig. 1. Symmetric branched cyanines of the monocationic series (**1** and **3**) and the dicationic series (**2** and **4**).

Reichardt and coworkers[1] for the synthesis of triple-branched cyanines with aromatic end groups. Thus, a reaction between CBr_4 and the enamine derived from dimethylamine and acetaldehyde was expected to lead to compound **3**. Similarly, condensation of triformylmethane with the corresponding imonium salt derived from dimethylamine and acetaldehyde was expected to give compound **4**. Reactions were attempted involving generating the enamine reagents *in situ*, since stable salts could not be prepared. As secondary amine, pyrrolidine was also tried in order to increase the reactivity of the enamine. No reaction was observed in either of these cases.

A second approach was to use the stable imonium salt derived from piperidine and acetaldehyde with $SnCl_6^{2-}$ as counter-ion.[7] This has been used in the synthesis of linear cyanines by condensation with merocyanines.[8] Attempts were made to induce reaction with CBr_4 in methanol using sodium methoxide as base, or with triformylmethane in acetic anhydride using pyridine as base, but the desired products were not obtained.

The successful route was found starting from known linear cyanine dyes. Arnold and Zemlicka[9] have shown that the symmetric dication **2** is formed in the Vilsmeier formylation with $COCl_2$/DMF of the 1,3-bis(dimethylamino)trimethinium cation (**5**) in the 2-position (Fig. 2), although it was not isolated as such. Arnold further showed[10] that in the formylation of the 1,5-bis(dimethylamino)pentamethinium cation (**6**) the attack also occurred in the 2-position to give the unsymmetric dication **7**, which was again not isolated. Finally, Holy and Arnold have reported[11] that formylation with $POCl_3$/DMF of the 1,7-bis(dimethylamino)heptamethinium cation **8** gave the 2,4-disubstituted derivative **10**, without, however, having isolated this quadruple-branched cyanine.

Since in this last procedure a five-fold excess of reagent had been used, we repeated it at lower temperature and with only a two-fold excess of reagent. We were able to isolate the 4-monosubstituted derivative **9** as yellow needles in 32 % yield. That selective mono-substitution at the central position is thus possible, came as no surprise, since we had already observed[12] that electrophilic bromination of the same cyanine gives cleanly the 4-monobromo derivative.

This promising observation of regioselectivity

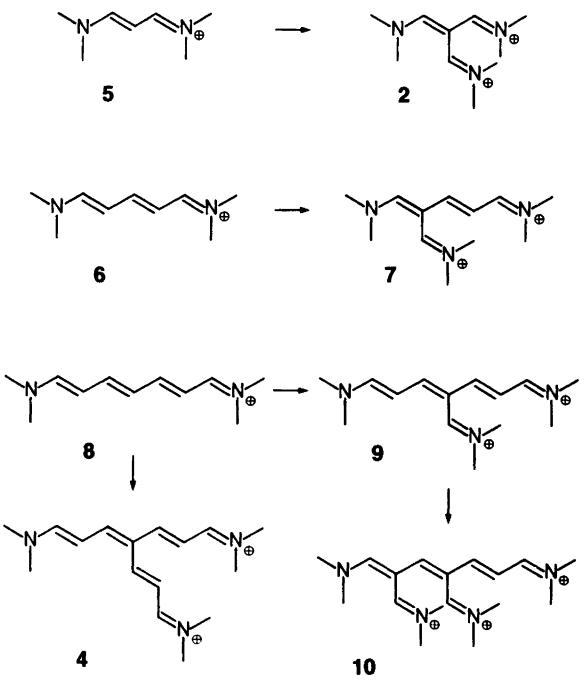

Fig. 2. Reaction products from unsubstituted cyanines (**5**, **6** and **8**) and DMF (or its vinylogue). Compounds **2**, **7** and **10** were reported as non-isolated intermediates by Arnold and coworkers (Refs. 9–11).

was followed up by an attempt to synthesize the dication **4** by an analogous electrophilic substitution of the same heptamethinium cation **8**, using the vinylogous Vilsmeier reagent prepared from 3-(dimethylamino)acrolein. This had previously been employed by Severin and Ipach[13] for the synthesis of 4-(dimethylamino)-1-nitro-1,3-butadiene, using dimethyl sulfate to generate the reagent. We used instead $POCl_3$ to prepare the active reagent, whose structure has been established as 3-(dimethylimonio)-1-chloropropene.[14] The desired triple-branched cyanine **4** was obtained as green prisms in 75 % yield and was the only isolated product even when the electrophilic reagent was used in excess.

For the synthesis of the monocation **3**, (Fig. 3) the branched trienediamine **15** was needed in order to attain the desired position of the branching and the desired length of the branch. With a 3-methyl substituent on the pentamethinium cation **14**, deprotonation converts the methyl group to a third and unhindered reactive site of the trienediamine **15**. Formylation using $POCl_3$/DMF had been reported by Arnold and Holy[15] to give the isolated triscation **16**, while with a more weakly activated reagent, viz. the dimethylacetal of DMF, the reaction stopped as expected after mono-formylation at the 3-methyl carbon. However, in this case no product was isolated or characterized, although a similar DMF-acetal reaction with the 1-methyl substituted trimethinium cation **11** gave selectively, and presumably via the dienediamine **12**, the expected and isolable triple-branched cation **13**.[15]

We have now repeated the reaction with the 3-methylpentamethinium cation (**14**) using the DMF-acetal, and had no difficulty in obtaining the triple-branched cyanine **3** as red needles in a yield of 65 % as the only isolated product.

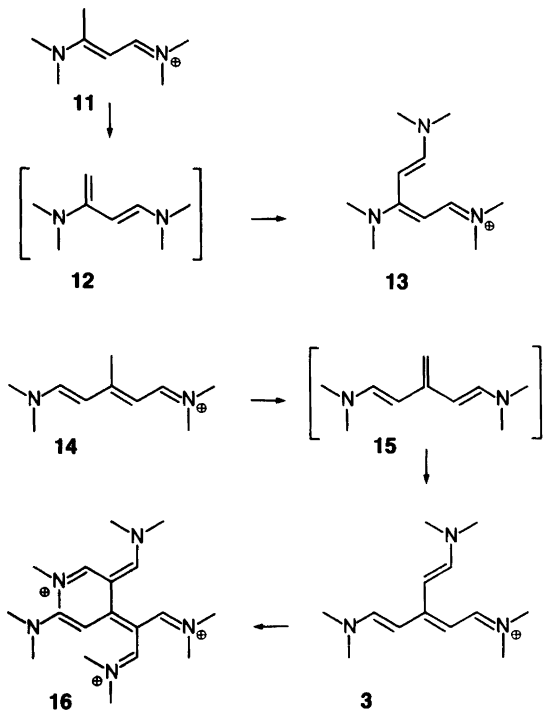

Fig. 3. Reaction products from methyl-substituted cyanines (**11** and **14**) and DMF. Compounds **13** and **16** were reported by Arnold and Holy (Ref. 15).

Conclusions

The origin of the presently observed regioselectivities in the Vilsmeier reaction, both with respect to the attack at the 4-position in the unsubstituted heptamethinium dye and the attack at the methyl carbon in the 3-methyl-substituted pentamethinium dye, is probably purely steric. The regioselective 4-bromination of the unsubstituted heptamethinium dye observed previously[12] is quite analogous. The 2-positions are in all cases, at least electronically, just as likely points of attack, but become severely hindered in the strongly preferred all-*trans* conformation or in any other conceivable planar conformation of cyanines.[16] Thus, the 2,4-dinitro derivative of the pentamethinium dye selects an entirely different non-planar conformation.[12]

Important conclusions concerning electronic charge distribution can be drawn from the observed ^{13}C chemical shifts for the unsaturated carbon atoms. It has previously been reported[19] that the ^{13}C shifts for simple linear cyanines show a dramatic alternation along the carbon chain (low-field signals for C-1, C-3 etc., high-field signals for C-2, C-4 etc.), and that this reflects nicely the calculated alternation of electron densities.[20] A similar alternation is observed for the present compounds (Fig. 4), whereby the central carbon becomes positively charged in mono-cations **1** and **3** but negatively charged in dications **2** and **4**. We have already used this as an argument for the mesomeric description of dication **2** with anionic

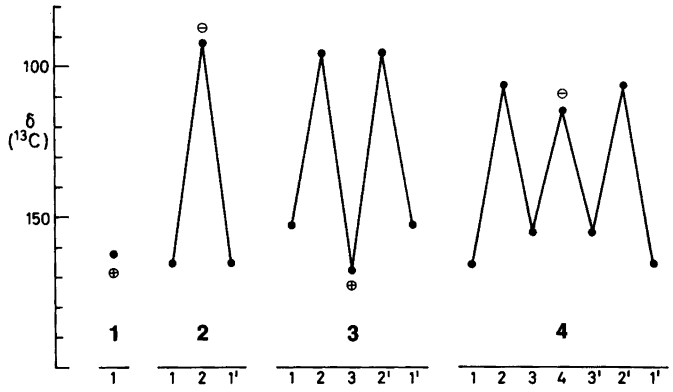

Fig. 4. ^{13}C NMR chemical shifts along the unsaturated chain of branched cyanines (**1–4**).

charge on the central carbon and positive charges on all three nitrogens, and for choosing this as a basis for the nomenclature.[6] The analogous choice is now made for dication **4**. Similar considerations form the basis of our present choice of nomenclature for the mono-cation **3**, since the electron density on C-3 is even lower than on C-1 (Fig. 4). This favours a mesomeric description of **3** with positive charge on the central carbon and none on the three nitrogens.

Dynamic NMR studies and X-ray structures of the branched cyanines **3** and **4** will be the subject of a separate paper.

Experimental

Tris(dimethylamino)methinium iodide (**1**). To a solution of *N,N,N',N'*-tetramethylguanidine in diethyl ether was added a large molar excess of methyl iodide. The precipitate was shown by NMR to consist mainly of a 1:1 mixture of hexamethylguanidinium iodide (**1**) and tetramethylguanidinium iodide. Repeated recrystallisation from ethanol gave pure hexamethylguanidinium iodide (**1**). Yield 40 % (max. 50 % based on guanidine), no m.p. below 350 °C (literature[21] 300 °C). ^{1}H NMR (300 MHz, CD_3OD): δ 3.10 (s); (DMSO-d_6): δ 2.89 (s). ^{13}C NMR (75 MHz, CD_3OD): δ 40.9 (6 NMe), 165.0 (C-1); (DMSO-d_6): δ 39.6, 162.4.

Tris(2-dimethylaminoethenyl)methinium perchlorate (**3**). A solution of 3-methyl-1,5-bis(dimethylamino)pentamethinium perchlorate[17] (4.4 g, 16 mmol) and dimethylformamide dimethylacetal (12 g, 100 mmol) in DMF (40 ml) was heated at 80 °C under nitrogen for 16 h. The solvent, together with excess of acetal, was evaporated in a rotary evaporator. The product was precipitated by addition of water (50 ml), filtered, and washed first with water and then with ethanol. Recrystallization from acetonitrile/ethanol (1:1) gave red needles. Yield 3.4 g (65 %), m.p. 214–215 °C. ^{1}H NMR (300 MHz, CD_3CN, 25 °C): δ 3.06 (18H, s, 6 NMe), 5.41 (3H, d, *J* 11.9 Hz, CH-2), 7.53 (3H, d, *J* 11.9 Hz, CH-1). ^{13}C NMR (75 MHz, CD_3CN, 25 °C): δ ~ 40 (broad, 6 NMe), 95.8 (C-2), 153.6 (C-1), 168.3 (C-3). UV (CH_3CN): 430 nm, log ε = 5.85.

Bis(3-dimethylimonio-1-propenyl)dimethylimoniomethylmethide diperchlorate (**9**). Phosphorus oxychloride (1.1 g, 7 mmol) was added dropwise to DMF (5 ml) cooled to 5 °C under nitrogen to DMF (5 ml) cooled to 5 °C under nitrogen atmosphere. The solution was then stirred for 30 min at room temperature. To this formylating reagent was added 1,7-bis(dimethylamino)heptamethinium perchlorate[18] (2.0 g, 7 mmol), and the mixture was stirred for 2 h. Addition of diethyl ether (50 ml) resulted in precipitation of an oil, which was washed with more ether. The oil was dissolved in methanol (20 ml), and $NaClO_4$ (1 g) was added to the solution. The resulting precipitate was filtered off, and recrystallization from acetonitrile/acetone (1:1) gave yellow needles. Yield 1.0 g (32 %), m.p. 236–238 °C. ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C): δ 3.36 (6H, s, NMe), 3.42 (3H, s, NMe), 3.47 (6H, s, NMe), 3.58 (3H, s, NMe), 6.51 (2H, dd, *J* 14.3, 10.6 Hz, CH-2), 7.87 (2H, d, *J* 14.3 Hz, CH-3), 8.22 (2H, d, *J* 10.6 Hz, CH-1), 8.39 (1H, s, CH-1'). ^{13}C NMR (75 MHz, DMSO-d_6, 25 °C): δ 39.4 (2

NMe), 43.4 (1 NMe), 47.1 (2 NMe), 48.9 (1 NMe), 106.0 (C-4), 106.5 (C-2), 156.0 (C-3), 161.8 (C-1′), 166.4 (C-1). UV (CH_3CN): 473 nm, log ε = 5.27.

Tris(3-dimethylimonio-1-propenyl)methide diperchlorate (**4**). To a solution of 3-dimethylamino-2-propenal (2.0 g, 20 mmol) in chloroform (30 ml) was added phosphorus oxychloride (2.8 g, 18 mmol) at 5 °C under a nitrogen atmosphere. The solution was then stirred for 30 min at room temperature. 1,7-Bis(dimethylamino)heptamethinium perchlorate[14] (2.6 g, 10 mmol) was added to the solution in one portion and the mixture was stirred for 1 h. The solvent was evaporated in a rotary evaporator, and to the residue was added a saturated solution of $NaClO_4$ in methanol (100 ml). The resulting precipitate was filtered off, and washed with water and methanol. Recrystallization from acetonitrile gave green prisms. Yield 3.2 g (75 %), m.p. 199–200 °C. ^{1}H NMR (300 MHz, DMSO-d_6, 30 °C): δ 3.36 (9H, s, NMe), 3.46 (9H, s, NMe), 6.68 (3H, dd, *J* 14.2, 10.7 Hz, CH-2), 8.10 (3H, d, *J* 14.2 Hz, CH-3), 8.23 (3H, d, *J* 10.7 Hz, CH-1). ^{13}C NMR (75 MHz, DMSO-d_6, 30 °C): δ 34.2 (3 NMe), 47.1 (3 NMe), 106.7 (C-2), 114.7 (C-4), 155.2 (C-3), 165.8 (C-1). UV (CH_3CN): 516 nm, log ε = 5.42.

Acknowledgement. We thank Norsk Hydro for financial support to O.I.E. through the *Senter for Industriforskning,* Oslo.

References

1. Reichardt, C. and Mormann, W. *Chem. Ber. 105* (1972) 1815.
2. Reichardt, C., Knecht, J., Mrosek, W., Plaas, D., Allmann, R. and Kucharczyk, D. *Chem. Ber. 116* (1983) 1982.
3. Allmann, R., Grahn, W., Knecht, J., Kucharczyk, D. and Reichardt, C. *Chem. Ber. 118* (1985) 1295.
4. Lecher, H. and Graf, F. *Ber. Dtsch. Chem. Ges. 56* (1923) 1326.
5. Arnold, Z. *Collect. Czech. Chem. Commun. 30* (1965) 2125.
6. Dale, J., Eriksen, O. I. and Groth, P. *Acta Chem. Scand., Ser. B 41* (1987) 653.
7. Lamchen, M., Pugh, W. and Stephen, A. M. *J. Chem. Soc.* (1954) 4418.
8. Nikolajewski, H. E., Dähne, S., Hirsch, B. and Jauer, E. A. *Chimia 20* (1966) 176.
9. Arnold, Z. and Zemlicka, J. *Collect. Czech. Chem. Commun. 25* (1960) 1318.
10. Arnold, Z. *Collect. Czech. Chem. Commun. 25* (1960) 1308.
11. Holy, A. and Arnold, Z. *Collect. Czech. Chem. Commun. 30* (1965) 53.
12. Dale, J., Krüger, S. and Rømming, C. *Acta Chem. Scand., Ser. B 38* (1984) 117.
13. Severin, T. and Ipach, I. *Chem. Ber. 111* (1978) 692.
14. Arnold, Z. and Zemlicka, J. *Collect. Czech. Chem. Commun. 24* (1959) 2378.
15. Arnold, Z. and Holy, A. *Collect. Czech. Chem. Commun. 28* (1963) 2040.
16. Dale, J., Lichtenthaler, R. G. and Teien, G. *Acta Chem. Scand., Ser. B 33* (1979) 141.
17. Köbrich, G. *Annalen 648* (1961) 114.
18. Nikolajewski, H. E., Dähne, S. and Hirsch, B. *Chem. Ber. 100* (1967) 2616.
19. Radeglia, R. *J. Prakt. Chem. 315* (1973) 1121.
20. Radeglia, R., Gey, E., Steiger, T., Kulpe, S., Lück, R., Ruthenberg, M., Stierl, M. and Dähne, S. *J. Prakt. Chem. 316* (1974) 766.

Received November 30, 1987.