Pure & Appl. Chem., Vol. 61, No. 9, pp. 1587–1592, 1989.
Printed in Great Britain.

Novel ligands designed for selective complexation of small cations

Johannes Dale* and Siw B. Fredriksen

Kjemisk Institutt, Universitetet i Oslo, N-0315 Oslo 3, Norway

Abstract - A variety of branched or macrocyclic polyether ligands of 1,5-dioxa type have been synthesized. Unsubstituted 12-crown-3 shows the strongest complexation, but lithium selectivity is lost due to the possibility of sandwich complexation of other cations. To sustain strong complexation of lithium, and to retain selectivity by preventing sandwich formation, it is necessary to introduce ligating side arms and to keep the number of methyl substituents as low as possible.

Glymes and crown-ethers of the common type, $-O-CH_2CH_2-O-$, have a natural geometry ("radius of curvature") that best fits medium-sized cations (Na^+, K^+, Ca^{2+}, Sr^{2+}, Ba^{2+}). The concept of "hole size" for crown-ethers is too simplistic, since a hole never exists without the cation, and not always even with the cation. Thus, no conformation with a significant hole can be found for 12-crown-4, and in its strong complex with Na^+ the cation is far outside the ring, actually sandwiched between two rings (ref. 1). Even Li^+ is clearly outside the ring in its weak 1:1 complex with 12-crown-4 (ref. 2).

Crown ethers with a longer carbon chain between heteroatoms, $-O-CH_2CH_2CH_2-O-$, should be able to fold more sharply back on small cations like Li^+ and Mg^{2+}. The obvious compound to test was the cyclic tetramer of oxetane, 16-crown-4. This had been obtained as early as 1956 by a British polymer chemist, J.B. Rose, in the BF_3 polymerization of oxetane (ref. 3). Polymer chemists at that time often limited themselves to following the disappearance of monomer and the appearance of precipitated polymer. Thus, in the polymerization of oxirane with BF_3 there is also formation of crown ethers (ref. 4), but since these are very soluble liquids or low-melting solids, they were for a long time not noticed. 16-Crown-4, on the other hand, is a less soluble and higher-melting solid, which could not remain undetected.

16-Crown-4 had interested us as part of our general studies on the conformation of macrocyclic compounds, and initially as the uncomplexed ring (ref. 5). IR- and X-ray studies (refs. 5,6) showed it to have the expected perfect square diamond-lattice conformation (Fig. 1) with two gauche $CH_2\ldots O$ interactions across each corner. This conformation is obviously not suited for complexation. Nevertheless, both this 16-ring and the analogous cyclic tetramer of 3,3-dimethyloxetane gave highly selective complexation of Li-salts, accompanied by a strong downfield shift (refs. 7,8) of the ^{13}C signals of α-CH_2 (12-crown-4 gives a strong upfield shift (ref. 1) on complexation). At low temperature the complexed 16-ring ligands gave splittings of the ^1H signals (refs. 7,8) that could be interpreted on the basis of a completely different ring conformation subsequently (ref. 9) verified by X-rays (Fig. 2).

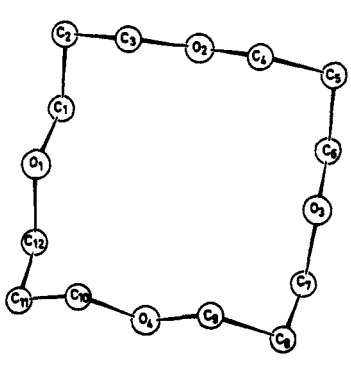

Fig. 1. 16-Crown-4.

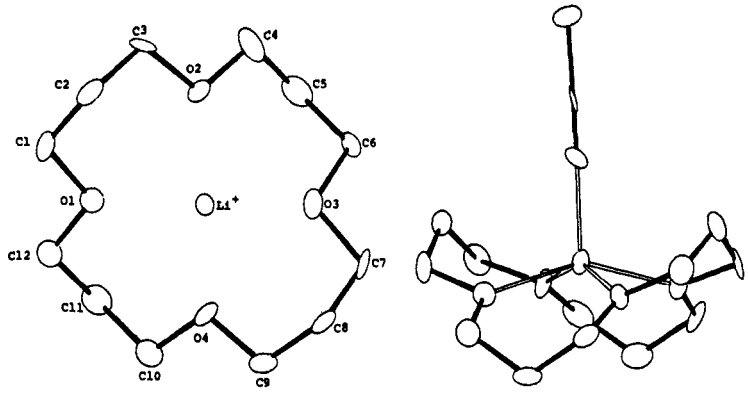

Fig. 2. LiNCS•16-crown-4.

The problem is that complexation, although selective, is very weak, so that it cannot compete with solvation in hydroxylic solvents. Acetonitrile or chloroform must be used. The main reason is probably the conformational stability of the free ligand that must be sacrificed to produce a complex. For the familiar crown ethers, like 12-crown-4, the situation is opposite: the best conformation for the ring skeleton can only be realized when the charge of a cation neutralizes the convergent ether-oxygen lone pairs. Since the alternative conformation chosen by the free ligand has some skeletal strain (ref. 10), this then represents a driving force for complexation.

That the 16-membered ring is formed so easily in the $-O-CH_2CH_2CH_2-O-$ system is not accidental. The conformation of the polymeric chain (Fig. 3) is extremely similar to that of the cyclic tetramer (ref. 11). The bends, or corners, are identical; the only difference being that gauche, gauche, signs (++ or --) are the same along the zig-zag polymer chain, but alternate in the square ring. Furthermore, we have recently found that short acyclic oligomers (ref. 12) crystallize with sign alternation at corners (ref. 13) and thus preform the ring structure and not the polymer structure (Figs. 5 and 6).

Again, the $-O-CH_2CH_2-O-$ system is different; if the anti, gauche, anti pattern of the polymer, with the same gauche sign along a given chain (Fig. 4), is changed into an alternating sequence, cyclic hexamer (18-crown-6) is produced (ref. 11). However, this diamond-lattice conformation is only stable as a cation complex, and a different one is chosen by the free ligand (Fig. 4).

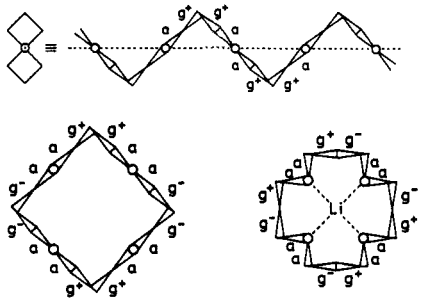

Fig. 3. Polymer and cyclic tetramer of oxetane.

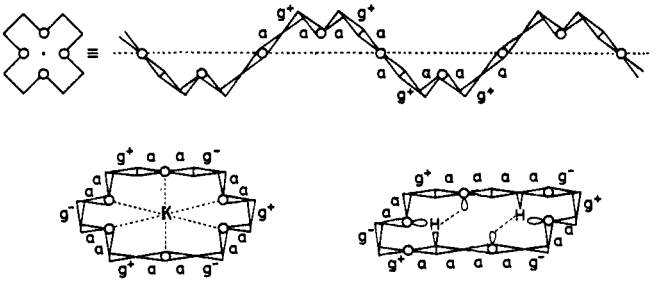

Fig. 4. Polymer and cyclic hexamer of oxirane.

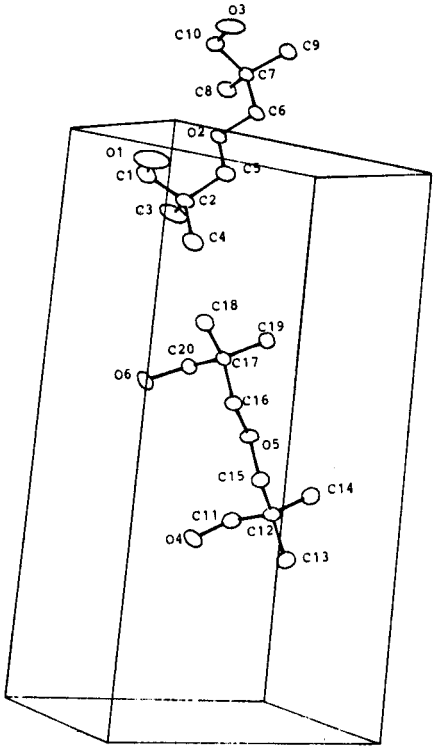

Fig. 5. Tetramethyl-4-oxaheptane-1,7-diol.

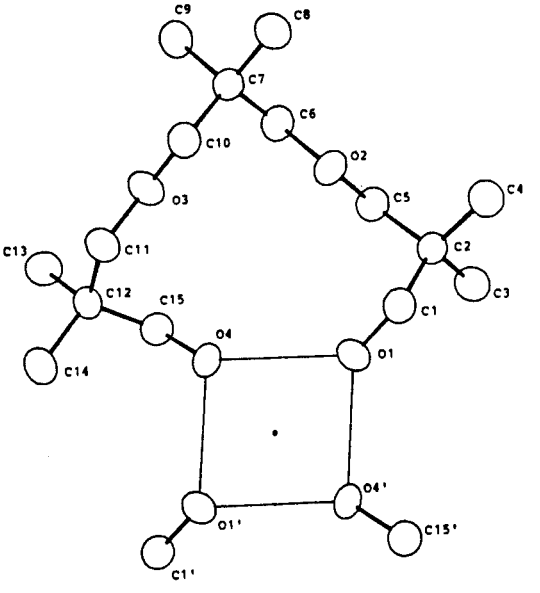

Fig. 6. Hexamethyl-4,8-dioxaundecane-1,11-diol.

As an aid in designing more successful ligands for Li^+ complexation we have made use of an "inspirational" molecular model. This was derived in a way that is reminiscent of another model that inspired the design of improved ligands for Na^+ complexation (refs. 14,15) and was based on the known crystal structure (ref. 1) for the sandwich complex of Na^+ with 12-crown-4. A completely encapsulated Na^+ with beautifully symmetric cubic octacoordination could then be imagined, the ligand being constructed from eight amino nitrogens linked by twelve $-CH_2CH_2-$ chains to give a quinquecyclic cage structure. From this model were then derived the various simpler amino-ether structures, of which a good number have been made and shown to be extremely strong and selective Na^+ complexers when at least one 12-ring is retained (refs. 14-17). In a similar way, we now start with the established crystal structure (Fig. 2) of the complex of Li^+ with 16-crown-4 (ref. 9). Addition of two $-CH_2-O-CH_2-$ bridges produces a tricyclic cage structure (Fig. 7, center) offering complete encapsulation of Li^+ with perfectly symmetric octahedral hexacoordination. This is the new model from which a variety of cyclic or branched-chain ligands can be derived (Fig. 7). They are all expected to fit cations the size of Li^+ and Mg^{2+}.

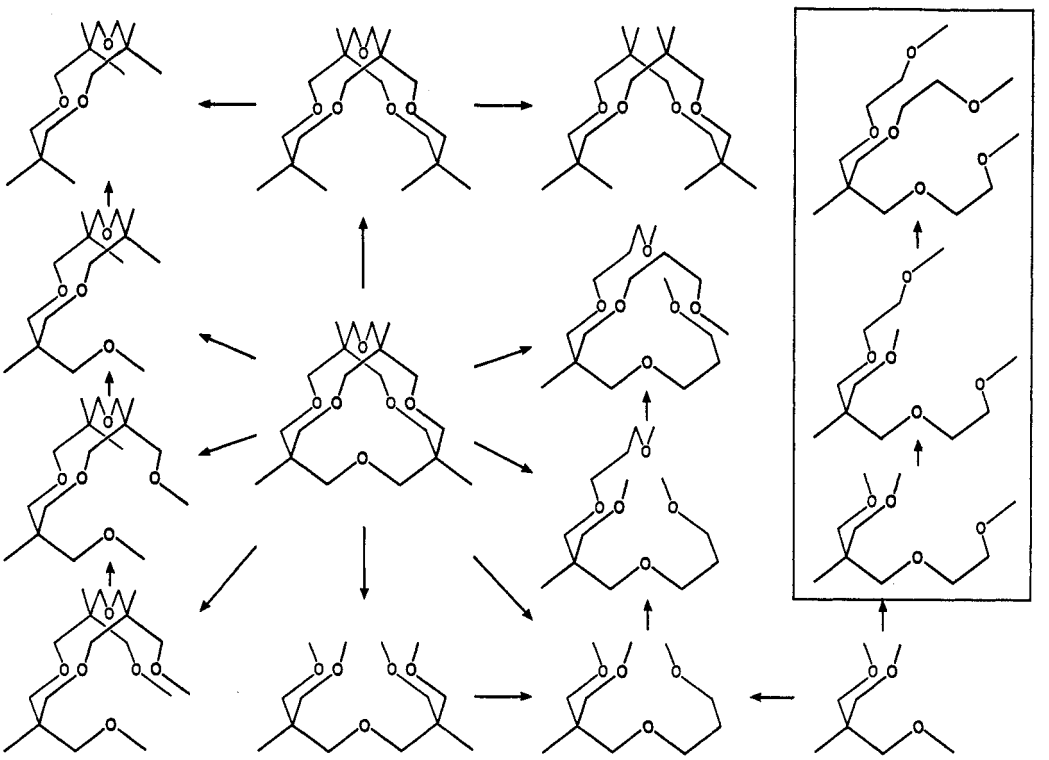

Fig. 7. Derivation of diamond-lattice ligand structures with octahedral coordination geometry.

The syntheses have been quite challenging and have led to interesting observations on reactivity (ref. 12), in particular a reversal of the famous neopentyl effect in substitution. This occurs when one or more of the methyl groups carry halogen or methoxy substituents (Fig. 8), the increased reactivity being explainable on the basis of neighbouring group participation (Fig. 9). Unfortunately, it turned out that open-chain ligands with only one branching point (Fig. 7) are much too weak complexers to be of interest, although they are specific for Li^+ against Na^+. Lengthening of one or two branches is beneficial, but lengthening also of the third has no further effect (ref. 12). Reasons are partly steric hindrance, but also the inherent conformational tendency to form a $g^{\pm}g^{\pm}$ "corner" instead of the $g^{\pm}g^{\mp}$ folding required for complexation. This was indicated by the mixed series (Fig. 7, framed column) where the branches were elongated by 1,4-dioxa units instead of 1,5-dioxa units (ref. 12). The complexation of Li^+ increased with each added unit to give finally a stronger Li^+-complexer, but now Na^+ starts to compete, resulting in loss of selectivity. A ligand with two branching points and only 1,5-related ether oxygens (Fig. 7, bottom) reached the same complexation level for Li^+ without complexing Na^+, but was still not sufficiently interesting (ref. 12).

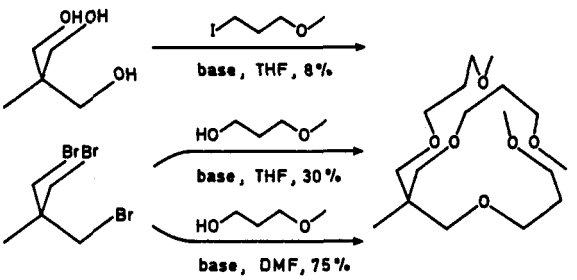

Fig. 8. Syntheses of a branched-chain ligand.

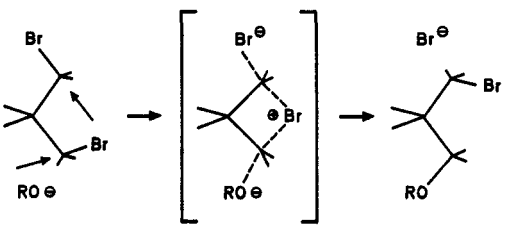

Fig. 9. Mechanism of facilitated neopentyl substitution.

It was then considered necessary to lock the proper geometry by keeping at least one 12-membered ring system intact. If necessary, it could carry one, two, or three side arms (Fig. 7, left column). For the synthesis of this ring system without ligating side arms, the cyclic trimerization of oxetanes suggested itself. It had already been noted that in addition to polymer and cyclic tetramer, pentamer, etc., also the cyclic trimer is formed in the BF_3 catalyzed reaction of oxetane, although only in trace quantities identified by GLC and MS. This reaction has now been optimized by lowering the concentration of monomer (ref. 18), although of cource real high-dilution conditions cannot be used in such an intermolecular reaction because of the decreased reaction rate. Initial concentrations were 0.05 M. From oxetane the best yield of 12-crown-3 (40%) was obtained with BF_3 in CH_2Cl_2, but at the expense of 16-crown-4 (<10%). Using PF_5 in CH_2Cl_2, the yield of trimer was lower and of tetramer higher. 3,3-Dimethyl-oxetane would give rise to a growing chain that is more restricted conformationally, and mainly octamethyl-16-crown-4 was produced in the presence of PF_5 in CH_2Cl_2 (70% tetramer, <1% trimer). Surprisingly, the BF_3/CH_2Cl_2 catalyst was very much slower, and BF_3 had to be renewed regularly. More cyclic trimer was now produced than tetramer, but at the same time a series of fluorohydrins (mostly the trimeric) was obtained, which explained the consumption of catalyst. By bubbling BF_3 through the reaction mixture after the monomer had been consumed, the fluorohydrins were converted to the corresponding cyclic products. Final yields of 20% of hexamethyl-12-crown-3 and 5% of octamethyl-16-crown-4 were thus obtained. An interpretation of these results is also based on the increased confor-

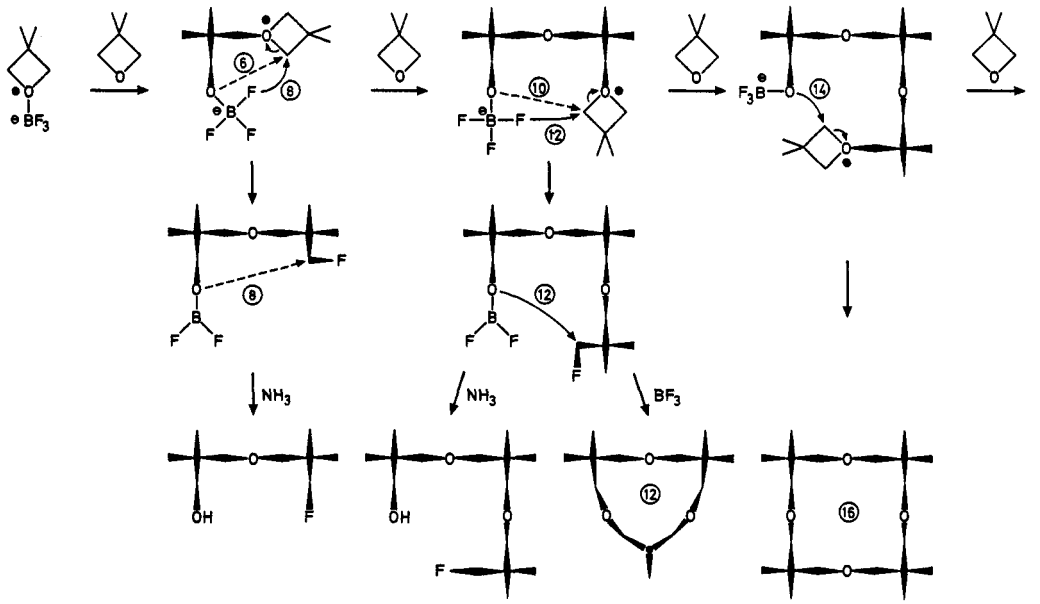

Fig. 10. Reaction scheme for 3,3-dimethyloxetane/BF_3.

mational restriction due to the gem-dimethyl groups. This would induce fluorine transfer when the transition state for cyclization becomes too strained (Fig. 10). The transition state for subsequent cyclization in the presence of additional BF_3 is less strained (ring size increased by two atoms, Fig. 10). The actual mechanism for the final cyclization may be stepwise or concerted (Fig. 11).

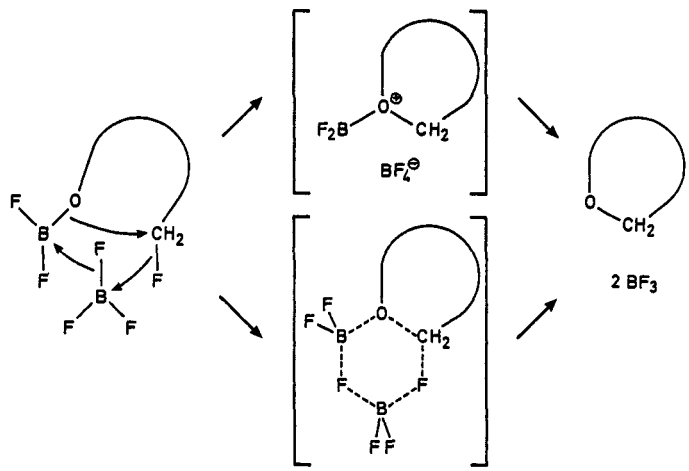

Fig. 11. Cyclization mechanism for fluorohydrin precursors with BF_3.

Complexation studies and X-ray determinations of crystal structures for 12-crown-3 and hexamethyl-12-crown-3 have already been reported (ref. 18). Both ligands when complexed with Li^+ adopt as expected the same unstrained diamond-lattice conformation (Figs. 12 and 13) excluded for the free ligands. Uncomplexed hexamethyl-12-crown-3 has a different and strained conformation as revealed by unusual torsion angles (Fig. 14). This strain represents an extra driving force for complexation and explains why 12-crown-3 ligands are stronger complexers than corresponding 16-crown-4 ligands. On the other hand, methyl groups interfere sterically so that the complexation strength is much reduced both for the methyl-substituted 12-ring and 16-ring (ref. 18). As a result, only unsubstituted 12-crown-3 has a satisfactory complexation strength, but unfortunately the selectivity for Li^+ is lost, since sandwich formation with larger cations becomes possible. Our present activity is therefore focused on multi-step syntheses of 12-crown-3 ligands having ligating methoxymethyl side-arms (Fig. 7, left column) and none, or fewer methyl substituents.

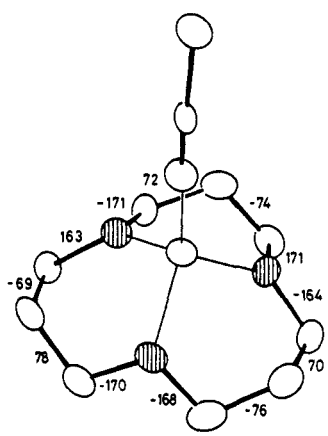

Fig. 12. LiNCS•12-crown-3.

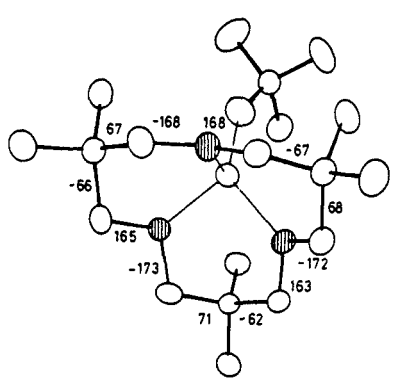

Fig. 13. $LiClO_4$•Me_6-12-crown-3.

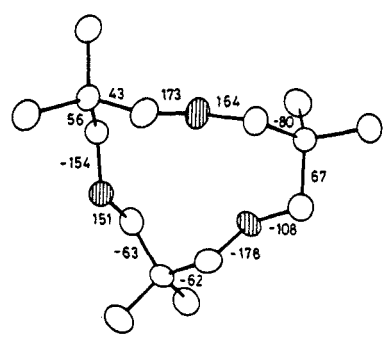

Fig. 14. Me_6-12-crown-3.

Acknowledgement

We thank Deminex (Norge)A/S for financial support to S.B.F. through the Senter for Industriforskning, Oslo.

REFERENCES

1. J. Krane, E. Amble, J. Dale and K. Daasvatn, Acta Chem. Scand., B34, 255-260 (1980).
2. P. Groth, Acta Chem. Scand., A35, 463-465 (1981).
3. J.B. Rose, J. Chem. Soc., 542-555 (1956).
4. J. Dale and K. Daasvatn, Acta. Chem. Scand., B34, 327-342 (1980).
5. G. Borgen and J. Dale, Chem. Commun., 1340-1342 (1970).
6. P. Groth, Acta Chem. Scand., 25, 725-734 (1971).
7. J. Dale and J. Krane, J. Chem. Soc. Chem. Commun., 1012-1013 (1972).
8. K.M. Aalmo and J. Krane, Acta Chem. Scand., A36, 219-225 (1982).
9. P. Groth, Acta Chem. Scand., A35, 460-462 (1981).
10. G. Borgen, J. Dale, K. Daasvatn and J. Krane, Acta Chem. Scand., B34, 249-254 (1980).
11. J. Dale, Tetrahedron, 30, 1683-1694 (1974).
12. S.B. Fredriksen, Thesis, University of Oslo (1985).
13. P. Groth, Acta Chem. Scand., B41, 487-493 (1987).
14. J. Dale, Colloque International du C.N.R.S. Composés Macrocycliques, Strasbourg (1982), p. I-1.
15. J. Dale, Oslo Symposium, Ion Exchange and Solvent Extraction, Soc. Chem. Ind. London (1982), p. III, 1-10.
16. T. Alfheim, S. Buöen, J. Dale and K.D. Krautwurst, Acta Chem. Scand., B40, 40-49 (1986).
17. S. Buöen and J. Dale, Acta Chem. Scand., B40, 141-144 (1986).
18. J. Dale, J. Eggestad, S.B. Fredriksen and P. Groth, J. Chem. Soc. Chem. Commun., 1391-1393 (1987).