Mechanism and Anion Activation in Solid–Liquid Phase-transfer Reactions Catalysed by Cyclophosphazenic Polypodands. Comparison with Cyclic Analogue Crown Ethers

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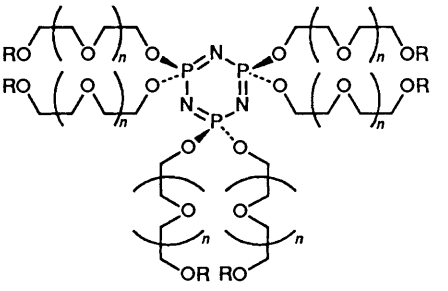
A kinetic study of the nucleophilic substitution of the methanesulfonic group by anions (Cl^-, Br^-, I^-, SCN^-, $C_6H_5O^-$, $C_6H_5CH_2COO^-$) catalysed by cyclophosphazenic polypodands has been performed under solid–liquid phase-transfer conditions. The results obtained show that the mechanism of PTC previously found for cyclic ligands (crown ethers, cryptands) also operates in the case of these open-chain ligands: the attack by the anionic nucleophile on the substrate occurs in the organic phase and is rate determining of the overall process. The nucleophilicity scales found ($I^- > C_6H_5O^- \approx SCN^- > C_6H_5CH_2COO^-$; $I^- > Br^- > Cl^-$) as well as the anion activation are comparable with those found for cyclic crown ethers. This indicates that the anionic reactive species involved are similar in the complexes of both ligands.

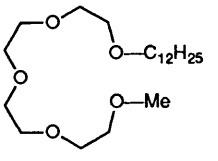
In previous reports we demonstrated that cyclophosphazenic polypodands **1a–c**, a new class of acyclic many-armed polyethers, are particularly efficient phase-transfer catalysts which combine high complexing capability in low polarity solvents with excellent chemical stability and ready availability.[1] As a consequence of their good complexing ability the catalytic activity of **1a–c** has proved to be much greater than that exhibited by other open-chain analogues like the simple podand **2** and TRIDENT **3**.[1,2] For this reason these polypodands could be used instead of the more expensive cyclic crown ethers, especially under solid–liquid phase-transfer catalysis (SL–PTC) conditions.

Whereas the mechanism of the reactions catalysed by cyclic ligands (crown ethers,[3] cryptands[4]) is now well defined, nothing is known about the behaviour of polypodands **1a–c** under the same conditions in spite of the growing interest in these open-chain ligands in organic synthesis.[1,2,5] Here we report a systematic study of the reaction mechanism and the anionic reactivity in a typical nucleophilic aliphatic substitution catalysed by cyclophosphazenic polypodands **1b, c** under SL–PTC conditions.†

A comparison of anion activation with the cyclic ligand perhydrodibenzo-18-crown-6 (PHDB-18-crown-6; **4**) is also included.



1a: $n = 2$; R = C_4H_9
b: $n = 3$; R = $C_{12}H_{25}$
c: $n = 4$; R = $C_6H_4C_8H_{17}$-*p*



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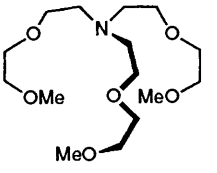

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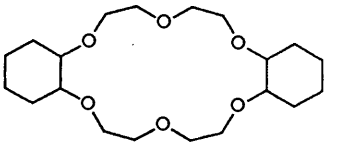

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Results

The rates of displacement of the methanesulfonic group in octyl methanesulfonate (**5**) by a series of anions Y^- (Cl^-, Br^-, I^-, SCN^-, $C_6H_5O^-$, $C_6H_5CH_2COO^-$) were measured at 60 °C in a solid–liquid MY salt–chlorobenzene two-phase system in the presence of catalytic amounts of **1b, c** ($0.2–4 \times 10^{-2}$ mol dm^{-3}) and with a 10:1 molar ratio of solid MY to substrate [reaction (1)].

$$\underset{\mathbf{5}}{n\text{-}C_8H_{17}OSO_2Me} + MY_{sol} \xrightarrow[C_6H_5Cl]{\mathbf{1b,c}_{(cat)}} \underset{\mathbf{6a–f}}{n\text{-}C_8H_{17}Y} + MeSO_3M_{sol} \quad (1)$$

M = Li, Na, K

Y = **a**, Cl; **b**, Br; **c**, I; **d**, SCN; **e**, C_6H_5O; **f**, $C_6H_5CH_2COO$

Reactions were carried out by magnetically stirring the heterogeneous mixture at 1200 ± 50 r.p.m., a value for which the rate constants were found to be independent of ion diffusion at the interface (see Table 1, footnote *e*).

Kinetic measurements were performed by GLC analysis following the disappearance of the substrate **5** and/or the appearance of the reaction products **6a–f**, in the presence of an internal standard (dodecane or tetradecane). They were found to obey the kinetic equation (2) up to at least three half-lives.

† The study was limited to ligands **1b** and **1c** which exhibited the highest complexation abilities and hence the best catalytic activities.[1]

Table 1 Second-order rate constants for the reaction of octyl methanesulfonate with Y^- anions under SL–PTC conditions catalysed by polypodands **1b**, **c** or PHDB-18-crown-6 (**4**), at 60 °C[a]

	1b		**1c**		PHDB-18-crown-6	
MY	Complexation extent[b,c]	$k^d/10^{-3}$ dm^3 mol^{-1} s^{-1}	Complexation extent[b,c]	$k^d/10^{-3}$ dm^3 mol^{-1} s^{-1}	Complexation extent[b,c]	$k^d/10^{-3}$ dm^3 mol^{-1} s^{-1}
LiBr			11	6.0	0.94	21.4
LiCl	0.29	0.37	0.22	0.42	0.12	1.9
NaI	4.1	11	4.0	10.6[e,f]	0.95	22
NaSCN	5.6	1.1	5.4	0.7	1.0	0.8
C_6H_5ONa			12	1.3	2.0	4.5
$C_6H_5CH_2COONa$			0.9	0.17	0.28	1.2
KI	0.6	4.5	0.5	4.0	1.0	10.7

[a] A chlorobenzene solution (10 cm^3) of substrate (0.2 mol dm^{-3}), catalyst (0.2–4 × 10^{-2} mol dm^{-3}) and internal standard (0.1 mol dm^{-3}) with 20 mmol of MY. [b] Defined as moles of complexed MY per mole of ligand. [c] Average of at least four determinations. The error in these values is estimated to be 10%. [d] Average of at least two determinations. The error in these values is estimated to be 5%. [e] The second-order rate constants obtained at lower stirring speed are 10.0 × 10^{-3}, 8.2 × 10^{-3} and 0.90 × 10^{-3} dm^3 mol^{-1} s^{-1} at 500, 300 and 50 r.p.m. respectively. [f] $\Delta H^{\ddagger}$ = 22.3 ± 0.4 kcal mol^{-1}; $\Delta S^{\ddagger}$ = −1.12 ± 0.8 e.u. calculated from the following rate constants: 3.2 × 10^{-3} at 50 °C; 10.6 × 10^{-3} at 60 °C and 25.2 × 10^{-3} dm^3 mol^{-1} s^{-1} at 70 °C.

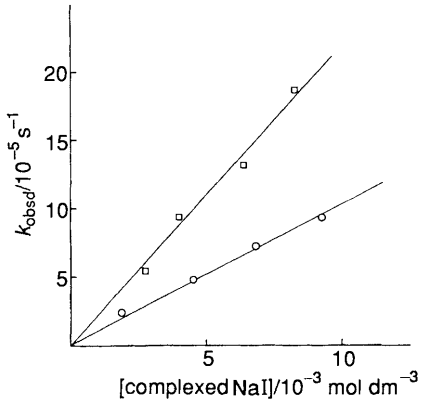


Fig. 1 Dependence of k_{obsd} on [complexed NaI] for reaction (1) catalysed by **1b** (○) or **4** (□)

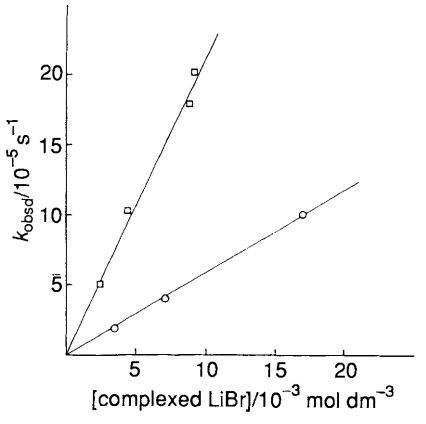


Fig. 2 Dependence of k_{obsd} on [complexed LiBr] for reaction (1) catalysed by **1b** (○) or **4** (□)

$$\text{rate} = k_{obsd}[\text{substrate}] \quad (2)$$

^{1}H and ^{31}P NMR analyses of the chlorobenzene solution showed that under the reaction conditions the polypodands **1b**, **c** are found entirely in the organic phase, in the free or complexed form (see Experimental section). Moreover titrimetric measurements indicated that no detectable amounts of the methanesulfonate ion are found in the organic phase under the reaction conditions. This means that the methanesulfonate is quantitatively released from the chlorobenzene solution so that equilibrium (3) is shifted fully to the right.

Table 2 Second-order rate constants for the reaction of octyl methanesulfonate (**5**) with anions Y^- associated with [(**1b**, **c**)⊃M^+], [(PHDB-18-crown-6)⊃M^+], in anhydrous chlorobenzene, at 60 °C[a]

	$k^b/10^{-3}$ dm^3 mol^{-1} s^{-1}		
MY	**1b**	**1c**	PHDB-18-crown-6
LiI	27	27	26.3
LiBr	3.3		12.7
LiCl	0.37	0.45	1.5
NaI	8.0	8.9[c]	19
NaSCN	0.80		0.81
C_6H_5ONa	0.84	0.89	5.6
$C_6H_5CH_2COONa$		0.20	1.51
KI	5.0	4.6	10.2

[a] [Substrate] = 1–4 × 10^{-2} mol dm^{-3}; [complexed MY] = 1–3 × 10^{-2} mol dm^{-3}. [b] Average of at least two determinations. The error in these values is estimated to be 5%. [c] $\Delta H^{\ddagger}$ = 19.7 ± 0.1 kcal mol^{-1}; $\Delta S^{\ddagger}$ = −9.13 ± 0.5 e.u. calculated from the following rate constants: 3.2 × 10^{-3} at 50 °C; 8.9 × 10^{-3} at 60 °C and 20.1 × 10^{-3} dm^3 mol^{-1} s^{-1} at 70 °C.

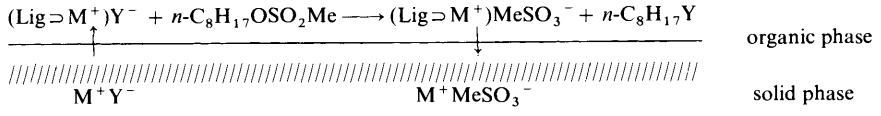
$$[(\text{Lig}\supset M^+)MeSO_3^-]_{org} + [Y^-]_{sol} \rightleftharpoons [(\text{Lig}\supset M^+)Y^-]_{org} + [MeSO_3^-]_{sol} \quad (3)$$

In the range examined (0.2–4 × 10^{-2} mol dm^{-3}) the observed rate constants are linearly related to the concentration of the complexed salt MY in the organic phase, as reported for **1b** and PHDB-18-crown-6 (**4**) in the case of NaI (Fig. 1) and LiBr (Fig. 2). The second-order rate constants (k_{obsd}/[complexed MY] dm^3 mol^{-1} s^{-1}) are reported in Table 1.*

The extent of complexation, defined as moles of complexed MY per mole of ligand, was determined by potentiometric titration of the anion Y^- in the organic phase. It remained constant during the reaction and was found to be in the range 0.2–12, depending on the nature of the salt. All these data are reported in Table 1 together with the corresponding results for PHDB-18-crown-6 (**4**) under the same conditions.

Kinetic measurements were also performed in anhydrous chlorobenzene with comparable concentrations of substrate (1–4 × 10^{-2} mol dm^{-3}) and complexed **1b**, **1c** or **4** (1–3 × 10^{-2} mol dm^{-3}) (Table 2).

* Blank experiments showed that the uncatalysed reactions are always much slower than catalysed ones (*e.g.* in the case of NaI the half-life is *ca.* 2 h in the presence of 0.0023 mol dm^{-3} **1c**, whereas without catalyst a conversion ≤ 1% was found after the same time.



Scheme 1

Rates were measured by potentiometric titration of the nucleophile, and reactions (4) were found to follow a second-order kinetic equation (5).

$$n\text{-}C_8H_{17}OSO_2Me\ (\mathbf{5}) + (Lig\supset M^+)Y^- \xrightarrow{C_6H_5Cl} n\text{-}C_8H_{17}Y\ (\mathbf{6a\text{–}f}) + (Lig\supset M^+)MeSO_3^- \quad (4)$$

$$\text{rate} = k[\text{substrate}][(Lig\supset M^+)Y^-] \quad (5)$$

The activation parameters, $\Delta H^{\ddagger}$ (kcal mol^{-1}) and $\Delta S^{\ddagger}$ (e.u.),* were calculated in the temperature range 50–70 °C for the reaction of octyl methanesulfonate (**5**) with NaI under both SL–PTC and homogeneous conditions. The obtained values are reported in Table 1, footnote *f* and Table 2, footnote *c*.

Discussion

Reaction Mechanism.—The kinetic behaviour observed in the nucleophilic substitution reaction (1) under SL–PTC conditions in the presence of catalytic amounts of cyclophosphazenic polypodands **1b** and **1c**† is analogous to that previously found for liquid–liquid phase-transfer reactions catalysed by cyclic ligands such as crown ethers[3] and cryptands.[4] In particular: (*i*) reactions follow regular pseudo-first-order kinetics, and the observed rate constants (k_{obsd}) are linearly related to the concentration of the complexed salt MY in the organic phase (Figs. 1 and 2); (*ii*) the presence of the substrate and of all the polypodand in solution excludes the possibility that the reaction takes place on the crystal surface; (*iii*) the second-order rate constants found under two-phase conditions are similar to those measured by using a homogeneous solution of the preformed complex $(Lig\supset M^+)Y^-$. So the values of the activation parameters $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ calculated in the case of NaI (Tables 1 and 2), are comparable in both systems. On the basis of these results the mechanism of the process can thus be proposed (see Scheme 1): the attack by the anionic nucleophile Y^- on the substrate occurs in the bulk of the organic solvent and is the rate-determining step, while the dissolution of the salt MY by the ligand and the release of the leaving group are relatively fast processes. The insignificance of interfacial phenomena is also confirmed by the non-dependence of the reaction rates on the stirring speed above 500 r.p.m. (Table 1).

Reactivity of Anions.—The nucleophilicity scale found for **1b**, **c** in the series of sodium salts ($I^- > C_6H_5O^- \approx SCN^- > C_6H_5CH_2COO^-$) is comparable for both ligands and is similar to that obtained by using PHDB-18-crown-6 (**4**) ($I^- > C_6H_5O^- > C_6H_5CH_2COO^- > SCN^-$) under SL–PTC conditions as well as homogeneous conditions (Tables 1 and 2). Analogously the sequence of reactivity measured in anhydrous chlorobenzene for lithium halides ($I^- > Br^- > Cl^-$) is the same for open-chain and cyclic ligands (Table 2).

The obtained trend is opposite to that usually found ($C_6H_5O^- > C_6H_5CH_2COO^- > Cl^- > Br^- > I^- > SCN^-$) for these anions in low polarity solvents where they are present as loose (quaternary salts)[6] or solvent-separated (cryptands)[4] ion pairs.‡

Such behaviour can be explained by assuming that in the complexes formed by polypodands **1b**, **c** the ligand does not induce a large charge separation in the ion pair: by increasing the charge density of the anion this ion pair becomes progressively more intimate and hence less reactive.

Anion Activation.—The complexation values found for **1b**, **c** (Table 1) are in general high, with unusual stoichiometries (up to 11–12 moles of MY per mole of ligand in the case of LiBr and C_6H_5ONa, respectively). These data seem to indicate the presence, in the molecular structure of these polypodands, of a certain number of pseudocavities, probably due to the diminished mobility of the polyethereal chains,[7] as confirmed also by molecular mechanics calculations.[8] The linear dependence of the observed rate constants (k_{obsd}) on the total amount of complexed MY (Figs. 1 and 2) suggests that the ion pairs in the complex all have the same reactivity which is, in turn, comparable with that of the corresponding single ion pair complexed by crown ether. Indeed, as shown in Tables 1 and 2, the anion activation exhibited by these acyclic many-armed ligands is of the same order or slightly lower than that obtained under the same conditions with the cyclic PHDB-18-crown-6 (**4**). Hence the cheaper cyclophosphazenic polyopodands **1b**, **c** can be considered a valid alternative to the more sophisticated cyclic systems, such as crown ethers, as anion activators.

Experimental

General Methods.—Potentiometric titrations were carried out with a Metrohm 670 Titroprocessor by using silver or glass and calomel electrodes, this last isolated with a potassium sulfate bridge. ^{1}H NMR spectra were performed on a Bruker AC300 spectrometer using tetramethylsilane as internal standard. ^{31}P NMR spectra were recorded on a Varian XL200 spectrometer using aqueous 0.06 mol dm^{-3} H_3PO_4 as an external reference. GLC data were obtained with an Alltech RSL-150 column (10 m × 0.35 mm polydimethylsiloxane, 0.25 μm thickness) or Superox II column (10 m × 0.35 mm polyethylene glycol, 0.25 μm thickness).

Materials and Solvents.—Salts MY (except C_6H_5ONa, $C_6H_5CH_2COONa$ and $MeSO_3M$) were Analar grade commercial products, used without further purification and kept in a dessicator. $MeSO_3M$ was prepared by neutralizing an aqueous solution of methanesulfonic acid with MOH and then evaporating the water under vacuum. $C_6H_5CH_2COONa$ was prepared analogously by neutralising an aqueous solution of phenylacetic acid with NaOH. C_6H_5ONa was prepared according to the literature.[9] Analar grade chlorobenzene was carefully purified and dried with standard methods.[10]

Octyl methanesulfonate (**5**), b.p. 112–114 °C at 2 mmHg, n_D^{20} 1.4398, was prepared according to the literature (lit.,[11] b.p. 110–

* 1 cal = 4.184 J; 1 e.u. = 4.184 J mol^{-1} K^{-1}.

† The results as a whole show that there are no significant differences in the behaviour of **1b** and **1c**: in particular complexation ability and kinetic data are the same within experimental error.

‡ In the case of cryptands the comparison is limited to halides and pseudohalides.

114 °C at 2 mmHg, n_D^{20} 1.4392). Cyclophosphazenic polypodands **1b**, **c** were prepared according to a previously reported procedure.[1b,12]

Determination of Extent of Complexation and Partition Coefficient.—The extent of complexation of polypodands **1b**, **c** and crown ether **4** under SL–PTC conditions was determined by stirring a standardized chlorobenzene solution of **1b**, **c** or **4** ($0.5–4 \times 10^{-2}$ mol dm^{-3}) and phenyl benzyl ether (0.1 mol dm^{-3}) (^{1}H NMR internal standard) with 100 molar equivalents of salt MY, as solid phase, in a flask thermostatted at 60 °C. The system was stirred for 1–2 h, then kept without stirring for an additional 10 min to allow good separation of the two phases. Aliquots (4–5 cm^3) of the organic phase were centrifuged, samples (2–3 cm^3) were withdrawn and titrated with 0.1 mol dm^{-3} $AgNO_3$ or 0.01 mol dm^{-3} HCl (potentiometric titration).

The partition of **1b** and **1c** under SL–PTC conditions was determined by ^{1}H and ^{31}P NMR measurements by checking the concentration of the ligands in the organic phase, before and after contact with the solid phase, with respect to an appropriate standard.

In the ^{1}H NMR spectra the areas of the aliphatic chains of the ligands [6(OCH_2–$C_{11}H_{23}$) for **1b** (138 H, δ 0.6–1.77) and 6(p-C_6H_4–C_8H_{17}) for **1c** (102 H, δ 0.4–1.80) were compared with that of the benzylic hydrogens (δ 4.8) of the internal standard phenyl benzyl ether. In the ^{31}P NMR spectra the area of the signal δ 18.4 [6P(OR)$_2$] was compared with that of a sample of known concentration (0.06 mol dm^{-3}) of aqueous H_3PO_4 as external standard. These measurements showed that the concentration of the ligand is unchanged after contact with the solid phase.

Kinetic Measurements.—In a typical procedure a standardized chlorobenzene solution (2 cm^3) of methanesulfonate (1 mol dm^{-3}) and internal standard (0.5 mol dm^{-3}) was added, in a flask thermostatted at 60 ± 0.1 °C, to a standardized solution (8 cm^3) of ligand (**1b**, **c** or **4**) ($0.25–5 \times 10^{-2}$ mol dm^{-3}) which had previously been stirred over solid MY (20 mmol) for 1 h, to obtain the complex formation. Timing and stirring were started. Aliquots of the organic phase were withdrawn (after stopping the stirring for 30–60 s to allow adequate separation) centrifuged, separated from any eventual solid precipitate and analysed by GLC (see *General Methods*).

The reaction rates were measured by following the disappearance and/or appearance of substrate and reaction product. The pseudo-first-order rate constants (k_{obsd}) were computer generated by plotting log [substrate] *vs.* time and determining the slope of the straight lines. The second-order rate constants k (dm^3 mol^{-1} s^{-1}) were evaluated by dividing k_{obsd} by the complexed MY concentration.

In the kinetic measurements under homogeneous conditions standardized chlorobenzene solutions (10 cm^3) of octyl methanesulfonate (**5**) ($5–20 \times 10^{-2}$ mol dm^{-3}) were added to a standardized solution (40 cm^3) of complexed MY ($1.5–4 \times 10^{-2}$ mol dm^{-3}) in a 100 cm^3 flask thermostatted at 60 ± 0.1 °C. The solution of preformed complex was prepared as described above. Samples (2–5 cm^3), withdrawn periodically, were quenched in ice-cold MeOH (50 cm^3) and the unreacted nucleophile Y^- was potentiometrically titrated (with 0.01 mol dm^{-3} $AgNO_3$ or HCl). The second-order rate constants were evaluated using a least-square computer program from the equation $1/([B_0] - [A_0])\ln([BA_0]/[AB_0]) = kt$, where A = substrate and B = complexed MY or *vice versa*. All rates involved at least 10 samplings and gave correlation coefficients of 0.997 or better.

The values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ in the temperature range 50–70 °C, were computer generated by plotting $\ln k/T$ *vs.* $1/T$, following the Eyring equation.

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References

1 (*a*) D. Landini, A. Maia, L. Corda, A. Maccioni and G. Podda, *Tetrahedron Lett.*, 1989, **30**, 5781; (*b*) *Tetrahedron*, 1991, **47**, 7477.
2 G. Soula, *J. Org. Chem.*, 1985, **50**, 3717.
3 D. Landini, A. Maia, F. Montanari and F. M. Pirisi, *J. Chem. Soc., Perkin Trans. 2*, 1980, 46; K. H. Wong and A. P. W. Wai, *J. Chem. Soc., Perkin Trans. 2*, 1983, 317.
4 D. Landini, A. Maia, F. Montanari and P. Tundo, *J. Am. Chem. Soc.*, 1979, **101**, 2526.
5 F. Vögtle and E. Weber, *Angew. Chem., Int. Ed. Engl.*, 1979, **18**, 753, and references therein; E. Weber and F. Vögtle, *Top. Curr. Chem.*, 1981, **98**, 1; F. Montanari, D. Landini and F. Rolla, *Top. Curr. Chem.*, 1982, **101**, 147; G. W. Gokel and S. H. Korzeniowski, 'Macrocyclic Polyether Syntheses' in *Reactivity and Structure Concepts in Organic Chemistry*, Springer-Verlag, Berlin, 1982, vol. 13, ch. 7; F. M. Menger, *Top. Curr. Chem.*, 1986, **136**, 1; T. E. Kron and E. N. Tsvetkov, *Russ. Chem. Rev. (Engl. Transl.)*, 1990, **59**, 283, and references therein; G. W. Gokel, 'Crown Ethers and Cryptands Monographs', in *Supramolecular Chemistry*, ed. J. F. Stoddart, University of Birmingham, UK, 1991.
6 D. Landini, A. Maia and F. Montanari, *J. Am. Chem. Soc.*, 1978, **100**, 2796; D. Landini, A. Maia and A. Rampoldi, *Gazz. Chim. Ital.*, 1989, **119**, 513.
7 F. Vögtle and E. Weber, *Angew. Chem., Int. Ed. Engl.*, 1974, **13**, 814.
8 A. Gamba, D. Landini, A. Maia, G. Morosi, G. Podda and A. Varnek, unpublished results.
9 N. Kornblum, P. J. Berrigan and W. J. Le Noble, *J. Am. Chem. Soc.*, 1963, **85**, 1141.
10 A. Riddick and W. B. Bunger in *Organic Solvents*, 2, 3rd edn.; ed. A. Weissberger, Wiley-Interscience, New York, 1970, pp. 767–768.
11 H. R. William and H. S. Mosher, *J. Am. Chem. Soc.*, 1954, **76**, 2984.
12 L. Corda, A. Anchisi, G. Podda, P. Traldi and M. Gleria, *Heterocycles*, 1986, **24**, 2821; G. Podda, *Gazz. Chim. Ital.*, 1988, **118**, 397.

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