Selective Acylation of Amines using 18-Crown-6

By ANTHONY G. M. BARRETT* and J. CARLOS A. LANA
(*Chemistry Department, Imperial College, London* SW7 2AY)

Summary Secondary dialkylamines were selectively acylated in the presence of primary amines by complexation of the latter with 18-crown-6 and a proton source.

CROWN ethers are widely applied in the complexation of both inorganic and organic salts.[1] 18-Crown-6 is able to complex primary alkylammonium salts by N–H · · · O

hydrogen bonding and $N^+ \cdots O$ interactions.[2] Typical stability constants[3] are in the order of 10^6 and complexation is probably diffusion controlled.[4] Since the cavity in 18-crown-6 is *ca.* 2·7 Å[2] secondary dialkylammonium salts are less efficiently complexed[5] (C.P.K. molecular models). Thus in a polyamine substrate selective transformations at a secondary amino function should be possible in the presence of 18-crown-6 and a proton source.

As model systems the acylation of benzylamine and *N*-alkyl-*N*-benzylamine mixtures have been examined (Table). In each case a dramatic increase in the ratio of secondary : primary acylation was achieved in the presence of 18-crown-6. Typically, triethylamine (dropwise over 10 min) and trifluoroacetic anhydride were added to a solution prepared from 18-crown-6, benzylamine, and *N*-benzyl-*N*-ethylammonium chloride (1 mmol each) in chloroform (1 ml). Chromatography on Merck Kieselgel 60 gave *N*-benzyl- and *N*-benzyl-*N*-ethyltrifluoroacetamides (98%). The blank reactions 1, 4, 7, and 10 (see Table) differed from the reactions with crown ether, being heterogeneous. In each case the secondary ammonium salts were as or more soluble than benzylammonium chloride (n.m.r.) and entries 13, 16, and 19 were all homogeneous. Clearly the selectivity resulted from complexation. The very hindered *N*-benzyl-*N*-t-butylammonium chloride was not significantly trifluoroacetylated in the presence of benzylamine and 18-crown-6 (1—2 equiv.).

Recently Stoddart has described the complexation of secondary dialkylammonium salts by *NN'*-dimethyldiaza-12-crown-4[6] and a diazadioxaparacyclophane.[7] The model reactions described here are currently being applied to polyamines.

TABLE

Entry No.	Amine salt	18-Crown-6 (equiv.)	% Amides	Secondary amide[b] (mol fractions)
(1)	*N*-Benzyl-*N*-methylammonium chloride	0	93	0·42
(2)	" " "	1	75	0·82
(3)	" " "	2	68(55)[c]	0·97
(4)	*N*-Benzyl-*N*-ethylammonium chloride	0	99(66)[d]	0·20
(5)	" " "	1	98	0·79
(6)	" " "	2	85(75)[e]	0·95
(7)	*N*-Benzyl-*N*-isopropylammonium chloride	0	94	0·06
(8)	" " "	1	93	0·41
(9)	" " "	2	99(63)[e]	0·63
(10)	*NN*-Dibenzylammonium chloride	0	(14)[e] (54)[f]	0·21
(11)	" " "	1	(62)[e] (29)[f]	0·60
(12)	" " "	2	(86)[e]	1·0
(13)	*N*-Benzyl-*N*-methylammonium toluene-4-sulphonate[g]	0	90(57)[d]	0·24
(14)	" " "	1	86	0·85
(15)	" " "	2	85	⩾0·98
(16)	" " "	0	100	0·67
(17)	" " "	1	94	0·93
(18)	" " "	2	96(80)[h]	⩾0·98
(19)	" " "	0	76	0·85
(20)	" " "	1	92	⩾0·98
(21)	" " "	2	94	⩾0·98

[a] Acylating agent: entries 1—15, $(CF_3CO)_2O$; entries 16—18, Ac_2O; entries 19—21, PhCOCl. [b] With the exception of entries 10, 11, and 12, ratios were estimated by n.m.r. spectroscopy (±0·02). All new compounds gave the expected microanalytical and spectral data. [c] Secondary amide isolated by distillation. [d] Primary amide isolated by crystallisation from toluene and cyclohexane. [e] Secondary amide isolated by chromatography on Merck Kieselgel H. [f] Primary amide isolated as in d. [g] Entries 13—21 carried out on 1 mmol scale using chloroform (10 ml). [h] Secondary amide isolated by recrystallisation from diethyl ether and cyclohexane.

We thank Capes, Brasilia, Brazil for financial support (to J.C.A.L.).

(*Received*, 3*rd March* 1978; *Com.* 221.)

[1] J. J. Christensen, D. J. Eatough, and R. M. Izatt, *Chem. Rev.*, 1974, **74**, 351.
[2] E. P. Kyba, R. C. Helgeson, K. Madan, G. W. Gokel, T. L. Tarnowski, S. S. Moore, and D. J. Cram, *J. Amer. Chem. Soc.*, 1977, **99**, 2564.
[3] J. M. Timko, S. S. Moore, D. M. Walba, P. C. Hiberty, and D. J. Cram, *J. Amer. Chem. Soc.*, 1977, **99**, 4207.
[4] F. deJong, D. N. Reinhoudt, and R. Huis, *Tetrahedron Letters*, 1977, 3985.
[5] C. J. Pedersen and H. K. Frensdorff, *Angew. Chem. Internat. Edn.*, 1972, **11**, 16.
[6] J. C. Metcalfe, J. F. Stoddart, and G. Jones, *J. Amer. Chem. Soc.*, 1977, **99**, 8317.
[7] H. F. Beckford, R. M. King, J. F. Stoddart, and R. F. Newton, *Tetrahedron Letters*, 1978, 171.