Effect of Crown Ethers on the Selectivity of Electrophilic Aromatic Nitration

Bernardo Masci

Centro C.N.R. di Studio sui Meccanismi di Reazione, c/o Dipartimento di Chimica, Università di Roma "La Sapienza", P.le Aldo Moro, 2 00185 Roma, Italy

Relative rates, isomer distributions, and partial rate factors have been determined for the nitration reactions of benzene, toluene, *m*-xylene, anisole, and mesitylene with tetrabutylammonium nitrate and trifluoroacetic anhydride in homogeneous CH_2Cl_2 solutions. The observed selectivity values have been compared with those obtained when 12-crown-4, 15-crown-5, 18-crown-6, 21-crown-7, or 24-crown-8 was added to the nitrating mixture. Small effects, if any, were observed with the smaller ligands, but marked variations in both substrate and positional selectivity appeared in the presence of 18-crown-6, 21-crown-7, and 24-crown-8. Such effects were found to depend on crown ether concentration and to vanish when $KClO_4$ was added. A reaction scheme is proposed where both uncomplexed and complexed nitronium ion contribute to variable extents to the overall reaction. The selectivity of the crown ether associated electrophile relative to the unassociated one seems to result from the balance of two different effects: an increase in the sensitivity to the electronic effects of the substituents and a larger crowding in the transition state. The largest effects on selectivity were observed with 21-crown-7 which causes ortho-para-directing groups to act as essentially para-directing groups. Data for toluene nitration in the presence of 21-crown-7 fit very well the Brown selectivity relationship, the selectivity factor spanning a remarkably wide range on changing the crown ether concentration.

Complexation of crown ethers with cations has been extensively used to increase the reactivity of the counterion:[1] much less evidence is available as to the influence of complexation on the reactivity of the complexed cation itself,[2] only the behavior of complexed aryldiazonium ions having been investigated in detail.[3]

Recently it has been reported[4] that crown ethers interact with NO_2BF_4 in a manner quite different from that of simple ethers. A strong and reversible interaction occurs, and the solution obtained by dissolving NO_2BF_4 with 21C7[5] in CH_2Cl_2 shows unprecedented selectivity features in the nitration of toluene and benzene. Complexation of NO_2-BF_4 by 18C6 and smaller crown ethers and altered selectivity in toluene–benzene nitration had been reported by Elsenbaumer and Wasserman,[6] while a third research group has worked on the 18C6–NO_2BF_4 system and has reported on the isolation of a 1:1 complex between the ligand and the salt.[7]

The present paper concerns itself with the quantitative definition of the effects of crown ethers on the selectivity of the nitration reaction, with the aim at understanding the mechanism of the action of the complexing agents. In this paper, the wide scope of the nitration reaction in the presence of crown ethers is demonstrated, and a rationalization is proposed for the peculiar selectivity behavior observed. The investigation covers the whole family of cyclic ligands from 12C4 to 24C8, in conjunction with a number of aromatic substrates ranging in reactivity from benzene to mesitylene. A mixture of trifluoroacetic an-

hydride (TFAA) and tetrabutylammonium nitrate in CH_2Cl_2 has been employed as the nitrating agent, which allows the nitration reaction to be performed in homogeneous solution even in the absence of crown ethers, at variance with preformed nitronium salts.

Results

All the work reported so far on the effect of crown ethers on the nitration reaction dealt with the reaction of NO_2BF_4 with toluene and benzene. A screening of several nitrating agents in organic solvents has shown that crown ethers influence the selectivity of the nitration reaction under a large variety of conditions.[8]

The mixture of Bu_4NNO_3 and TFAA in CH_2Cl_2 has been chosen to carry out a more extensive investigation due to its several merits, namely, mild reaction conditions, clean mononitration of the investigated substrates, suitably fast rates of reaction, and magnified effects of crown ethers on selectivity. This nitrating system is a modification of that reported by Crivello,[9] which consists of TFAA and heterogeneous metal or ammonium nitrates in inert solvents. The presence of the tetrabutylammonium counterion does not introduce any complication in the reaction. Bu_4NNO_3 is very soluble in CH_2Cl_2 and CH_2Cl_2 plus TFAA, and the large Bu_4N^+ cation, unlike ammonium and alkali metal cations, can hardly associate with the crown ethers.

Benzene, toluene, *m*-xylene, anisole, and mesitylene have been chosen as the aromatic substrates: for them such complications as ipso attack are expected to be unimportant,[10a] and a number of selectivity data can be found in the literature[10] for comparison purposes.

The general working procedure was as follows. Equimolar amounts of pairs of aromatic substrates (toluene/

(1) (a) Liotta, C. L. In "Synthetic Multidentate Macrocyclic Compounds" Izatt, R. M., Christensen, J. J., Eds.; Academic Press: New York, 1978; p 111. (b) de Jong, F.; Reinhoudt, D. N. *Adv. Phys. Org. Chem.* 1980, *17*, 279.

(2) For some pioneering work in this field, see: Kyba, E. P.; Helgeson, R. C.; Madan, K.; Gokel, G. W.; Tarnowski, T. L.; Moore, S. S.; Cram, D. J. *J. Am. Chem. Soc.* 1977, *99*, 2564.

(3) Bartsch, R. A. In "Progress in Macrocyclic Chemistry"; Izatt, R. M., Christensen, J. J., Eds.; Wiley: New York, 1981; Vol. 2, p 1.

(4) Masci, B. *J. Chem. Soc., Chem. Commun.* 1982, 1262.

(5) The shorthand notations 21C7, 12C4, etc. will be used throughout this paper to indicate 21-crown-7, 12-crown-4, etc.

(6) (a) Elsenbaumer, R. L.; Wasserman, E. *Abstr. Pap—Chem. Congr. North Am. Cont. 2nd* 1980, Abstr. 77. (b) Elsenbaumer, R. L.; Wasserman, E. U.S. Patent 4 392 978, 1983.

(7) Savoie, R.; Pigeon-Gosselin, M.; Rodrigue, A.; Chénevert, R. *Can. J. Chem.* 1983, *61*, 1248.

(8) Unpublished results from this laboratory.

(9) Crivello, J. V. *J. Org. Chem.* 1981, *46*, 3056.

(10) (a) For extensive discussion of quantitative studies on aromatic nitration, see: Schofield, K. "Aromatic Nitration"; Cambridge University Press: Cambridge, U.K., 1980. For some selective nitrations more recently reported, see: (b) Olah, G. A.; Fung, A. P.; Narang, S. C.; Olah, J. A. *J. Org. Chem.* 1981, *46*, 3533. (c) Olah, G. A.; Narang, S. C.; Olah, J. A.; Lammertsma, K. *Proc. Natl. Acad. Sci. U.S.A.* 1982, *79*, 4487. (d) Dinctürk, S.; Ridd, J. H. *J. Chem. Soc., Perkin Trans. 2* 1982, 965. (e) Olah, G. A.; Narang, S. C.; Olah, J. A.; Pearson, R. L.; Cupas, C. A. *J. Am. Chem. Soc.* 1980, *102*, 3507.

Table I. The Effect of the Crown Ether Size on the Selectivity of Aromatic Nitration with Bu₄NNO₃–TFAA in CH₂Cl₂ at 25 °C[a]

substrate	no crown ether	12C4	15C5	18C6	21C7	24C8
toluene						
k_{rel}[b]	57.5	59.0	57.7	65.7	127	58.3
% o-NO₂	57.2	57.4	56.5	47.1	15.1	24.9
% m-NO₂	1.89	2.04	2.14	1.90	1.22	2.29
% p-NO₂	40.9	40.6	41.3	51.0	83.7	72.9
m-xylene						
k_{rel}[b]	833	980	1010	1670	1190	511
% 2-NO₂	15.7	14.4	13.6	8.5	5.6	10.7
% 4-NO₂	84.3	85.6	86.4	91.5	94.4	89.3
anisole						
k_{rel}[b]	2100	2660	3430	23600	26300	3350
% o-NO₂	78.0	77.4	70.9	16.4	4.6	27.5
% p-NO₂	22.0	22.6	29.1	83.6	95.4	72.5
mesitylene						
k_{rel}[b]	4390	5040	5860	12400	3380	2060

[a] The crown ether concentration at the end of the dropwise addition was 0.115 M. [b] Rate constant values relative to benzene.
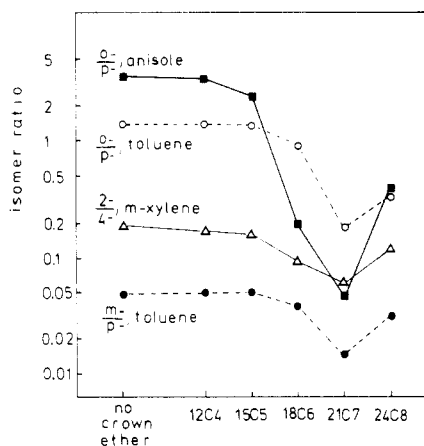

Figure 1. The change in isomer distribution on varying the size of the crown ether in the nitration reaction of aromatics with Bu₄NNO₃–TFAA in CH₂Cl₂ at 25 °C.

benzene, m-xylene/toluene, anisole/m-xylene, and mesitylene/anisole) were reacted in competitive kinetic experiments with the nitrating mixture either in the presence or in the absence of crown ethers. As the aromatics were always in large excess with respect to the nitrating agent, the relative rates were directly obtained by the molar ratios of the nitrated products; these ratios and the isomer distributions were determined by gas chromatographic analysis of the reacted solution. All the reactivity data could be referred to benzene and expressed as partial rate factors.

The effect of the size of the crown ether on substrate and positional selectivity is shown by the data in Table I. These were obtained from reactions run by dropwise addition of 0.15 mL of a CH₂Cl₂ solution of Bu₄NNO₃ (0.120 M), TFAA (0.86 M), and n-eicosane as an internal standard (2.12 × 10⁻² M), with no crown ether or in the presence of a fixed amount of crown ether (0.42 M), to a 0.40-mL CH₂Cl₂ solution of a pair of aromatics (both 1.18 M).

Small effects if any are observed in the presence of 12C4 and 15C5, whilst both relative rates and isomer distributions are strongly altered by the presence of 18C6, 21C7, and 24C8. The observed isomer ratio as a function of the ring size of the ligand is represented in Figure 1, and the combined data of positional and substrate selectivity are represented in Figure 2 as partial rate factors.

A more detailed analysis of the behavior of added 18C6 and 21C7 has been carried out by running the competitive kinetic experiments at varying concentrations of the lig-
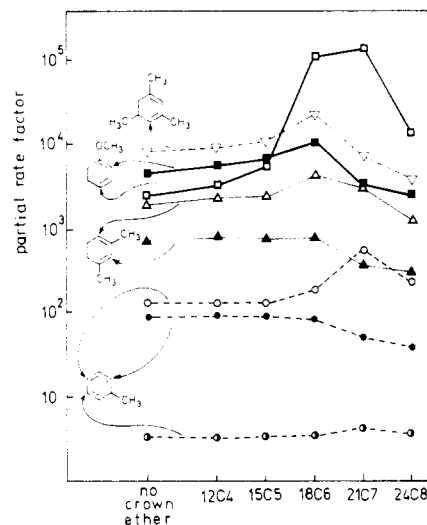

Figure 2. The effect of the size of the crown ether on the partial rate factors in the nitration of aromatics with Bu₄NNO₃–TFAA in CH₂Cl₂ at 25 °C.
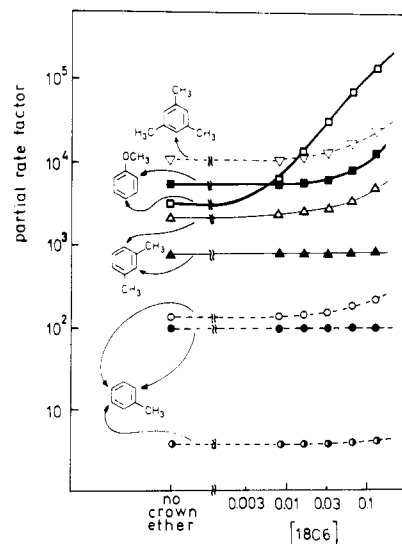

Figure 3. The effect of 18C6 concentration on the partial rate factors in the nitration of aromatics with Bu₄NNO₃–TFAA in CH₂Cl₂ at 25 °C.

ands. In these experiments the same conditions as described above were used, but the nitrating mixture was added all at once in order to have better defined concentration conditions in the reacting system.[11] Table II lists

Table II. The Effect of Crown Ether Concentration on the Selectivity of the Nitration Reaction with Bu$_4$NNO$_3$-TFAA in CH$_2$Cl$_2$ at 25 °C

substrate	no crown ether	[18C6], M					[21C7], M					
		0.0082	0.0164	0.0328	0.0655	0.131	0.0041	0.0082	0.0164	0.0328	0.0655	0.131
toluene												
k_{rel}[a]	56.0	57.1	58.4	58.2	64.7	71.0	56.3	61.3	73.1	81.4	114	127
% o-NO$_2$	58.0	56.9	56.0	55.2	51.2	47.3	54.2	50.1	38.3	30.6	18.9	14.1
% m-NO$_2$	2.13	2.12	2.02	2.04	2.00	1.84	2.00	1.86	1.71	1.58	1.27	1.24
% p-NO$_2$	39.9	41.0	42.0	42.7	46.8	50.9	43.8	48.1	60.0	67.8	79.8	84.7
m-xylene												
k_{rel}[a]	816	898	952	1020	1280	1800	860	891	1010	1030	1190	1270
% 2-NO$_2$	15.2	14.8	13.5	12.2	10.2	7.6	14.8	14.0	12.0	10.0	6.8	5.0
% 4-NO$_2$	84.8	85.2	86.5	87.8	89.8	92.4	85.2	86.0	88.0	90.0	93.2	95.0
anisole												
k_{rel}[a]	2220	2790	4030	7140	14800	26400	3170	4940	8300	10800	18900	27600
% o-NO$_2$	78.1	64.7	46.7	27.3	17.5	13.3	50.2	33.8	21.3	13.2	6.5	4.8
% p-NO$_2$	21.9	35.3	53.3	72.7	82.5	86.7	49.8	66.2	78.7	86.8	93.5	95.2
mesitylene												
k_{rel}[a]	5240	5510	5550	6380	8600	12200	4510	5640	5070	4530	4260	4690

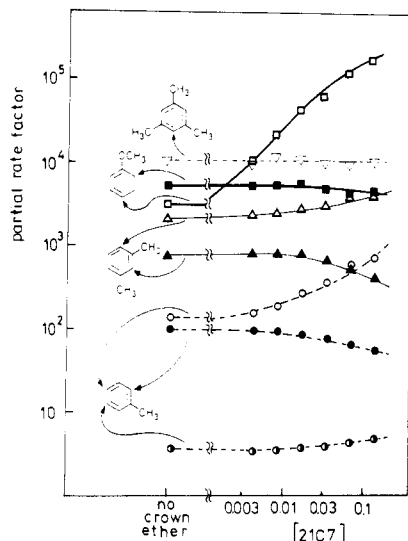[a] Rate constant values relative to benzene.

Figure 4. The effect of 21C7 concentration on the partial rate factors in the nitration of aromatics with Bu$_4$NNO$_3$-TFAA in CH$_2$Cl$_2$ at 25 °C.

the relative rates and isomer distributions at the various ligand concentrations. The profiles of the partial rate factors as a function of crown ether concentration are shown in Figures 3 and 4 for 18C6 and 21C7, respectively.

A set of experiments have been carried out, using the last described addition procedure, to ascertain the effect of additional species on selectivity. The data, which are shown in Table III, can be compared with those in Table II. It is apparent that a large concentration of 18C6 has almost no effect on the selectivity of Bu$_4$NNO$_3$-TFAA if an equivalent amount of KClO$_4$ is present. On the other hand, although 21C7 failed to solubilize a stoichiometric amount of KClO$_4$ in CH$_2$Cl$_2$, a set of reactions run in the presence of 0.089 M 21C7 and 0.058 M KClO$_4$ showed a selectivity pattern corresponding to a low 21C7 concentration. The last column in Table III refers to reactions in which a 10% concentration KNO$_2$ is added to a nitrating mixture, [21C7]/[Bu$_4$NNO$_3$] = 1. The selectivity data are little affected, as expected, for the sequestration of a small quantity of crown ether by K$^+$, but no additional effect of NO$_2^-$ is apparent.

A preliminary investigation has shown that also the absolute rate of the nitration reaction is markedly influ-

Table III. The Effect of Added KClO$_4$ and KNO$_2$ on the Selectivity of the Nitration Reaction with Bu$_4$NNO$_3$-TFAA and Crown Ethers in CH$_2$Cl$_2$ at 25 C

substrate	18C6 + KClO$_4$[b]	21C7 + KClO$_4$[c]	21C7 + KNO$_2$[d]
toluene			
k_{rel}[a]	57.0	67.3	99.0
% o-NO$_2$	60.1	45.8	22.8
% m-NO$_2$	2.20	1.96	1.58
% p-NO$_2$	37.7	52.2	75.6
m-xylene			
k_{rel}[a]	781	766	1130
% 2-NO$_2$	13.8	10.4	7.7
% 4-NO$_2$	86.2	89.6	92.3
anisole			
k_{rel}[a]	2170	7210	15000
% o-NO$_2$	74.7	20.2	9.3
% p-NO$_2$	25.3	79.8	90.7
mesitylene			
k_{rel}[a]	3690	6580	4030

[a] Rate constant values relative to benzene. [b] [18C6] = 0.115 M, [KClO$_4$] = 0.115 M. [c] [21C7] = 0.089 M, [KClO$_4$] = 0.058 M. [d] [21C7] = 0.0655 M, [KNO$_2$] = 0.011 M.
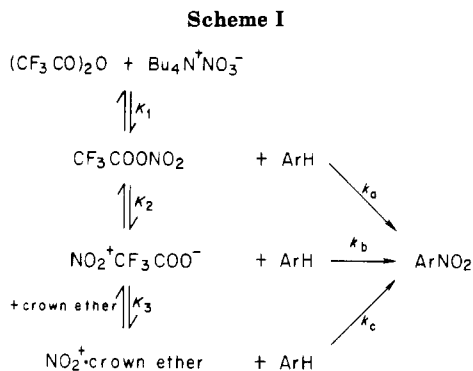
enced by the nature and concentration of the crown ether, large rate retardations being observed at high ligand concentrations.[12]

Discussion

Many features of the nitration reaction of activated substrates continue to elude a firm definition: the subject is debated[10] mostly in connection with the nature of the reacting species and of the nature of the intermediates which are thought to precede the formation of the σ adduct. Clearly, the effect of crown ethers cannot be fully understood if the mechanism of the reaction in their absence is not well-known. However, at the present stage of advancement of the subject, we need not enter the most controversial points: it is sufficient to note that such problems as leveling of reaction rate contrasted by high positional selectivity, which are frequently met in nitration of activated substrates,[10a] occur only to a limited extent in the reaction conditions here reported. In fact, such conditions have been chosen as to observe selectivity in all the examined activation range, even for the reaction in the absence of crown ethers. Actually the reaction with Bu$_4$NNO$_3$-TFAA in CH$_2$Cl$_2$ at 25 °C is among the most selective nitration reactions reported,[13] the relative rates

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(11) However, no significant difference in selectivity is apparent when data obtained with the two different techniques are compared.

(12) Work is in progress to obtain a comprehensive set of absolute rate data.

Scheme I

$$(CF_3CO)_2O \ + \ Bu_4N^+NO_3^-$$

$$\Big\Updownarrow K_1$$

$$CF_3COONO_2 \qquad + \ ArH$$

$$\Big\Updownarrow K_2 \qquad\qquad\qquad \searrow^{k_a}$$

$$NO_2^+CF_3COO^- \ + \ ArH \ \xrightarrow{k_b} \ ArNO_2$$

$$+crown\ ether\Big\Updownarrow K_3 \qquad\qquad \nearrow^{k_c}$$

$$NO_2^+\cdot crown\ ether \quad + \ ArH$$

being similar to those observed in some instances with HNO_3 in Ac_2O[14] and somewhat lower than those observed with HNO_3–Ac_2O in CH_2Cl_2 at $-25\ °C$.[15]

The results of the present work clearly show that the effect of crown ethers on the selectivity of aromatic nitration is not limited to reactions run with preformed nitronium salts. Bearing in mind the effect of crown ethers on the solubility of NO_2BF_4 in CH_2Cl_2, the selectivity of the nitrating mixtures so obtained in the nitration of toluene and benzene, the isolation of a $18C6\cdot NO_2BF_4$ complex, and the many additional evidences of complexation,[4,6,7] it is very likely that also in the nitrating system considered in this work the formation of complexes with nitronium ion is the cause of the changes in selectivity.

Let us briefly examine the possibilities depicted in Scheme I: a mixed anhydride, which can in principle be reactive, originates from the added reagents, whereas very reactive electrophilic species (free and/or ion-paired NO_2^+ ion) are formed according to equilibrium K_2. The crown ether can complex these salts and alter the reaction rate by shifting the equilibria K_1 and K_2 and subtracting the reacting species (equilibrium K_3). If the reaction path k_c is not a productive one, the same selectivity is expected both in the presence and in the absence of crown ethers. A similar occurrence, namely a rate-retarding effect with about no influence on the product distribution, has been reported for the well-known thermal stabilization of diazonium salts with crown ethers.[3] A very interesting situation is met if k_c contributes appreciably, for in this case changes in selectivity are expected to take place. The results of the present work clearly show this is the case. Namely, different selectivity patterns are observed on varying the crown ether size and concentration, the data relative to the crown ethers which are known[4] to easily complex nitronium salts being quite different from each other and from those obtained in the absence of crown ethers. Moreover, for a given crown ether quite different effects on selectivity are observed for different substrates or for different positions of the same substrate. So, on inspection of Figure 2 a number of contrasting situations are apparent: for instance, some partial rate factors are definitely lower in the presence of 21C7 than in the absence of crown ethers, whereas $p_f^{OCH_3}$ is up to almost 2 powers of 10 higher. Also the sensitivity of the selectivity to the crown ether concentration depends on the nature of the crown ether itself, as shown by Figures 3 and 4. That any conclusion drawn from observations performed at only one ligand concentration cannot be safe is well illustrated by
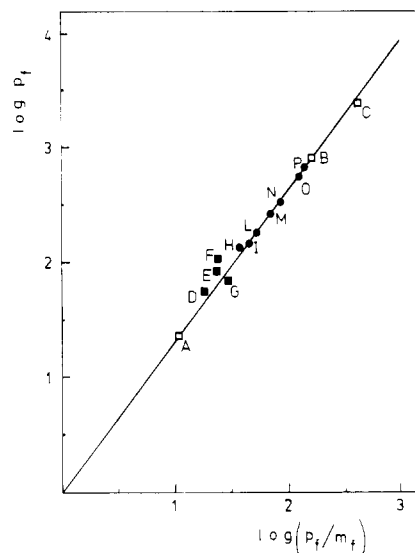
Figure 5. The varying selectivity of the nitration reaction of toluene and the fit to the Brown's selectivity relationship. Representative data for electrophilic aromatic substitution reactions (□): (A) mercuration with $Hg(OAc)_2$ in AcOH;[19] (B) chlorination with Cl_2 in AcOH;[20] (C) bromination with Br_2 in 85% AcOH (Brown, H. C.; Stock, L. M. *J. Am. Chem. Soc.* **1957**, *79*, 1421). Representative data for nitration reactions taken from the literature (■): (D) with $AgNO_3$–BF_3 in CH_3CN;[10b] (E) with *N*-nitro-2,4,6-collidinium tetrafluoroborate in CH_3CN;[10e] (F) with HNO_3 in Ac_2O;[14] (G) with HNO_3 in AcOH (Olah, G. A.; Kuhn, S. J.; Flood, S. H.; Evans, J. C. *J. Am. Chem. Soc.* **1962**, *84*, 3687). Data from the present work, Table II (●): (H) no crown ether present; (I, L, M, N, O, and P) in the presence of 21C7, at concentrations 4.1×10^{-3}, 8.2×10^{-3}, 1.64×10^{-2}, 3.28×10^{-2}, 6.55×10^{-2}, and $0.131\ M$ (respectively). All data were obtained at 25 °C. The slope of the straight line is 1.31.[17]

the behavior of $p_f^{OCH_3}$: at low concentration 21C7 markedly enhances selectivity and 18C6 quite moderately, but at high concentration very similar partial rate factors are observed.[16] Actually each combination of size and concentration of crown ether results in a particular selectivity behavior, and this seems to be different for the various substrates and positions of attack.

Nonetheless a number of regularities are apparent, and a rationalization is possible by assuming that the addition of crown ethers changes the nitrating species into others which are more sensitive to both the electronic and the steric effects of the substituents. Let us examine Figure 4 and consider in the order for 21C7 the attack to positions with no ortho substituent, the attack to positions with only one ortho substituent, and the series of methylbenzenes as a whole. Finally, in the light of the above points, a comparison will be made among the various ligands.

For the attack to the meta and para positions of toluene and to the para position of anisole an increase in selectivity is observed on increasing 21C7 concentration, and the effect is higher with the higher the activating power of the substituent: m-CH_3 < p-CH_3 < p-OCH_3. Actually, for toluene nitration a quantitative expression can be given to the above correlation, as illustrated in Figure 5, where the close fit to the Brown's selectivity relationship[17] (BSR) is shown for reactions carried out in the presence of varying concentrations of 21C7. The fit suggests that for toluene nitration, substrate and positional selectivities are determined in the same reaction step, as it happens in a well-

(13) The properties of the reactions with Bu_4NNO_3–TFAA in connection with the other nitrations in organic solvents will be commented on in a forthcoming paper.

(14) (a) Hartshorn, S. R.; Moodie, R. B.; Schofield, K. *J. Chem. Soc. B* **1971**, 1256. (b) Hartshorn, S. R.; Moodie, R. B.; Schofield, K.; Thompson, M. J. *J. Chem. Soc. B* **1971**, 2447.

(15) Stock, L. M.; Young, P. E. *J. Am. Chem. Soc.* **1972**, *94*, 4247.

(16) On extrapolating the observed values, even an inversion of the order of selectivity can be expected to occur at higher ligand concentrations.

(17) Stock, L. M.; Brown, H. C. *Adv. Phys. Org. Chem.* **1963**, *1*, 35.

behaved electrophilic aromatic substitution. Apart from the mechanistic implications, which will be better dealt with, for toluene and more activated substrates, when absolute rate data will be available,[12] the data in Figure 5 deserve a further comment. Namely they show how the moderately selective reaction of toluene nitration, which is observed with most nitrating agents reported in the literature[10,18] (some representative cases are shown), can be transformed into a quite selective one in the presence of 21C7. So, the selectivity factor[17] $S_f = \log (p_f/m_f)$ which usually ranges between 1.2 and 1.6, can be made as high as 2.14: that is the nitration reaction of toluene, from being only slightly more selective than mercuration with Hg(O-Ac)$_2$ in AcOH,[19] becomes almost as selective as chlorination with Cl$_2$ in AcOH.[20]

If we now go back to Figure 4 and consider the attack to positions with only one ortho substituent, we observe that almost no effect is brought about by 21C7 on $o_f^{OCH_3}$, and a definite decrease on $o_f^{CH_3}$. As an electronic effect similar to that experienced for the attack to the para positions is expected, it must be admitted that besides the electronic effect, a steric effect operates which disfavors the substitution reaction in the ortho position with respect to that on benzene.

For *m*-xylene and mesitylene nitration, the effects of the several o-CH$_3$ and p-CH$_3$ groups must be combined. So, when partial rate factors are considered, the attack to the 2 position of *m*-xylene should be somewhat more disfavored by 21C7 than the attack ortho to toluene, the attack to the 4 position somewhat less favored that the attack para to toluene, and the attack to mesitylene little affected as this situation differs from the attack to the 2 position of *m*-xylene by the presence of an additional p-CH$_3$ group. As the effects of the various methyl groups on the nitration carried out in the absence of crown ethers are not additive,[21] no more than a roughly qualitative correlation is expected to hold for the effects of 21C7 calculated with respect to that reference reaction, and within these limits a satisfactory agreement with the experimental results is observed.

When different crown ethers are considered, it is noted that the profiles in Figure 3 differ from those in Figure 4 under several respects; in particular no decrease in selectivity is observed on adding 18C6, and partial rate factors for nitromesitylene and o-nitroanisole formation definitely increase. On the other hand, Figure 2 shows that partial rate factors observed in the presence of 24C8 are always lower than those obtained in the presence of 21C7, and that moderate increases with respect to the reaction run in the absence of crown ethers only occur for the attack to unhindered positions. In all cases the BSR holds, the values of $(\log p_f^{CH_3})/\log (p_f^{CH_3}/m_f^{CH_3})$ being 1.34–1.35 for 18C6 and 1.42 for 24C8, and the combination of the effects exerted by 18C6 or 24C8 on toluene nitration yields in general a satisfactory agreement with the selectivity observed for polymethylbenzenes. Then the selectivity data for all the crown ether sizes can be interpreted as proposed above for 21C7; what actually vary are the quantitative values of the electronic and steric effects. If we assume that the relative importance of the steric effect with respect to the electronic one can be simply measured by the changes in partial rate factors for the attack ortho to toluene or anisole, the scale 24C8 > 21C7 > 18C6 can be

established. As to the absolute value of the electronic effect, which seems in principle to be measured by the increased selectivity for the unhindered positions, an unambiguous order cannot be established.[22]

The most interesting effect of the presence of crown ethers in the nitration reaction is that on positional selectivity. Namely, as a consequence of different trends in partial rate factors for the less and the more sterically hindered substitution product, marked changes in isomer distribution are observed in several cases. The effect (Figure 1) is particularly strong in the presence of 21C7 which apparently produces both a marked increase in the sensitivity to the electronic effects and a considerable steric hindrance in the transition state. In the presence of high concentrations of 21C7 only small quantities of o-nitrotoluene, 2-nitro-1,3-dimethylbenzene, and o-nitroanisole are produced. The handicap imposed by 21C7 to substitution in the ortho position is currently being observed on several substrates.[8] As a general behavior, ortho–para-directing groups turn out to act as essentially para-directing groups in the nitration of monosubstituted benzene derivatives.

Summing up, the complicated overall picture of the results presented in this work can be interpreted as follows. The changes in selectivity on increasing crown ether concentration can be accounted for by an enhanced importance of the reaction path k_c relative to k_b in Scheme I,[23] the shape of the profiles in Figures 3 and 4 being determined by the values of k_c and K_3 for the given ligand. In the presence of crown ethers the reaction becomes more sensitive to the electronic effects of the substituents, but the transition state which contains the ligand is more sterically hindered, and the attack to positions adjacent to groups other than hydrogen is disfavored with respect to the attack to benzene. The value of k_c for the attack to a single position of a given substrate results from the balance of the electronic and the steric effect.

Admittedly, the above interpretation based on Scheme I may turn out to be oversimplified; that it is sound in its main features is further supported by check experiments, while a number of evidences are against some different explanations of the results. The quantitative recovery of the added crown ether at the end of the reaction supports the reversible nature of the interaction between NO$_2^+$ and the ligand. On the other hand, the inhibition of the effect of crown ethers on selectivity when KClO$_4$ is added also supports this point and ensures that the effect of crown ethers on selectivity is not due to trace impurities added with the ligand. Moreover the absence of appreciable effects of added nitrite ion seems to rule out the possibility that such large inversions of the ortho/para ratio in the nitration of anisole are due to the presence of low-valent nitrogen impurities in the nitrating mixture.[24]

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(20) Brown, H. C.; Stock, L. M. *J. Am. Chem. Soc.* **1957**, *79*, 5175.

(21) This feature is shared with all the nitration reactions reported in the literature.[10]

(22) 21C7 gives the largest increases in partial rate factors, but the relative position of 24C8 and 18C6 is different for toluene and anisole nitration. Seldom can a general validity be attached to an observed order of crown ether efficiency: see preceding and ref 16.

(23) Strictly speaking the good fit to the BSR requires that only one electrophilic species is active at a given crown ether concentration, which is in contrast with the suggested reaction scheme, considering, the parallel reaction paths k_b and k_c. Actually, provided that both the reaction going through k_b and that going through k_c obey the BSR, a deviation from the straight line can hardly be observed for the overall reaction. For instance, were the selectivity factors for the two reactions 1.4 and 2.4 (ρ values of −5.7 and −9.8, respectively) and each one to contribute to a half of the overall reaction, the point for the observed reaction should lie on a line of slope 1.27 instead of 1.31.

(24) Nitrosation followed by oxydation can often be held responsible for the anomalous selectivity of nitration of highly activated aromatics;[10] on the other hand, it is to be noted that in the present work quite unusual selectivities are observed even in toluene nitration.

It is possible that problems connected with macroscopic and/or microscopic diffusion[10a],[25] play a role in the reaction run with only Bu_4NNO_3-TFAA on the more activated substrates, where the observed substrate selectivity is rather low. It is to be noted that in the presence of the larger crown ethers the enhancement of the substrate selectivity as determined by the partial rate factors for sterically unhindered positions is significative in the whole activation range and is always paralleled by an enhanced regioselectivity. This behavior cannot be due to simple prevailing mixing problems as a consequence of the lowering of the reaction rate.

On the other hand, in the presence of the larger crown ethers not only the reactivity of anisole and mesitylene is clearly activation controlled, but also the selectivity of toluene nitration is significatively affected. That is, what is observed is not a simple shift in the limit of the substituents activating power required for an encounter control of the rate; such a shift could be caused by changes in the medium composition, but these should be about the same whatever the added crown ether is.

Concluding Remarks

A regulation of the selectivity of the nitration reaction can be operated over a remarkably wide range by properly choosing the concentration and the nature of crown ethers.

Besides offering the obvious practical advantage of achieving high regioselectivities in such an important reaction as nitration is, the effect of crown ethers is interesting from a mechanistic point of view. Namely, a nitration reaction performed in homogeneous solution shows a distinguished behavior with respect to all the other reported nitration reactions, and yet its features are those of a well-behaved electrophilic aromatic substitution.

A simple distribution scheme considering the effectiveness of both uncomplexed and complexed nitronium ion in the nitration reaction seems to account for the large variety of behaviors displayed by the selectivity in the presence of crown ethers. For a more quantitative analysis and a deeper insight into the mechanism of the action of crown ethers, absolute rate data are needed for the reaction in the absence and in the presence of the complexing agents.

Experimental Section

Materials. The crown ethers used in this kind of work must be very pure, particularly when they are used at high concentrations. Less pure ligands produced low conversion into nitro derivatives.

The following chemicals were used as received: Bu_4NNO_3 and 1,2-bis(2-chloroethoxy)ethane (Fluka purum); TFAA (Fluka purum, Fluka puriss., Merck); 2-chloroethyl ether (Aldrich); diethylene glycol, triethylene glycol, toluene-4-sulfonyl chloride, *m*-xylene, and mesitylene (Erba RP). Benzene, toluene, and anisole were purified by fractional distillation on a 45 theoretical plates Todd column; 15C5 (Aldrich) and 12C4 and 18C6 (Fluka purum) by distillation under vacuum on a Buchi Spaltrohr apparatus. Heptaethylene glycol was prepared according to a published procedure.[26] Commercial CH_2Cl_2 was shaken with concentrated H_2SO_4, washed with water, dried over anhydrous Na_2SO_4, and then distilled from phosphorus pentoxide through a 50-cm Vigreux column.

Octaethylene Glycol. Octaethylene glycol was obtained from triethylene glycol (4.5 mol), 2-chloroethyl ether (0.75 mol), and NaOH (1.5 mol) by adapting a procedure reported for heptaethylene glycol.[26] The exceeding triethyl glycol was distilled off, bp ca. 140 °C (0.8 mmHg), and fractional distillation in a short Claisen apparatus gave 89 g (32% yield) of the desired product, bp 220–234 °C (0.4 mmHg), which was checked to be 94% pure

by GLC, the contaminating products being the homologues from hexa- to nonaethylene glycol. By redistillation a purer product (96%) was obtained.

24-Crown-8. 24C8 was prepared by adapting the method developed by Okahara et al.[27] Octaethylene glycol (22.7 g, 0.061 mol, 96% pure) and 11.7 g (0.061 mol) of TsCl in 30 mL of dioxane were added over 10 h to a stirred suspension of 16 g (0.24 mol) of powdered KOH[28] in 300 mL of dioxane heated at 75 °C: the addition was performed by means of a syringe operated by a Sage Instruments syringe pump 355. Stirring and heating were continued overnight. The yield of 24C8 was checked to be 36% (GLC) after filtering the cooled mixture and repeated washing of the residue with CH_2Cl_2. The residue obtained after removal of the solvent was heated up to 270 °C (internal temperature) under vacuum and 10 g of colorless oil collected, most product boiling at 170 °C (0.4 mmHg). The distilled material was then extracted with several portions of light petroleum (total volume 250 mL) and the obtained solution cooled (down to −20 °C) in order to have a crystalline purified product, which was transferred to a precooled gooch crucible through a bent glass tube fitted into rubber stopcocks under pressure of argon. The residual solvent was removed under vacuum, and 6.0 g of 24C8 was obtained. This was 97% pure by GLC, 27-crown-9 being the most abundant impurity, and melted at 22.5–24.5 °C, the only previously reported value being significantly lower (19 °C).[29]

21-Crown-7. 21C7 was prepared, as described before for 24C8, from heptaethylene glycol (0.061 mol) in 57% yield (by GLC). The distilled material was purified by complex formation on addition of CH_3NO_2. 21C7 (5.8 g), 98% pure by GLC, was obtained on removing CH_3NO_2 under vacuum from the filtered complex.

The purity of the crown ethers and of the intermediates for their preparation was checked by GLC on a 50 cm × $^1/_8$ in. stainless steel column packed with 5% OV 101 on G. H. P. 100–120 Chromosorb.

Competitive Kinetic Measurements and Product Analysis. The nitrating mixture was prepared by adding via a syringe TFAA to a precooled CH_2Cl_2 solution of Bu_4NNO_3, *n*-eicosane, and crown ether in a septum-capped vessel. The mixture was allowed to stand 5 min at 25 °C, and then 0.15-mL aliquots were taken with a syringe and added into a septum-capped vessel containing the stirred solution of the aromatics maintained at 25 ± 1 °C. The dropwise addition was completed in ca. 30 s. Precautions to avoid moisture were taken in all the above operations.

The reacted mixtures were analyzed by GLC after at least 20 min, either by direct injection or after a workup with saturated $NaHCO_3$ followed by treatment with water and drying over Na_2SO_4. The GLC response factors were determined by analyzing mixtures of known amounts of nitro derivatives or of nitro derivatives and *n*-eicosane. *m*-Nitroanisole could not be detected in the reaction products (less than 5/10 000 parts with respect to the ortho and para isomers), while 5-nitro-1,3-dimethylbenzene was not searched for.

The analyses were performed on a Hewlett-Packard 5830A gas chromatograph, equipped with a 18850A terminal and flame ionization detector, using either a 3 m × $^1/_8$ in. stainless steel column packed with 10% SP 1000 on 80-100 Supelcoport, or a 2 m × $^1/_8$ in. glass column packed with 10% carbowax 20 M plus 2% KOH on WAW Chromosorb 80-100.

The reproducibility of the results was quite good. The data in Table I are the mean values from two to three independent runs carried out with different purity grade samples of TFAA, different workup procedures, and different GLC columns. No systematic trend was observed in the selectivity values on changing the above conditions, the mean deviation calculated for the relative rates in Table I and for the partial rate factors calculated therefrom being generally well within 15% (only five values between 15% and 30%).

Conversions of Bu_4NNO_3 into mononitro derivatives were generally in the range 70–90%. Check experiments run in typical cases with an aromatic substrate at low concentration, namely,

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(26) Krespan, C. G. *J. Org. Chem.* **1974**, *39*, 2351.

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(28) No appreciable improvement in the yield of 24C8 was observed in small-scale experiments on substituting CsOH for KOH.

(29) Dale, J.; Kristiansen, P. O. *Acta Chem. Scand.* **1972**, *39*, 1471.

[Ar] = [Bu₄NNO₃], showed that the incomplete conversion into mononitro derivatives was paralleled by the presence of unreacted starting substrate, so that at least 93% of the starting material could be accounted for.

In a number of cases it has been checked by GLC that the added amount of crown ether (1:1 molar ratio with respect to Bu₄NNO₃) can be found unchanged in the reacted mixture.

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Reactions of Maleic Anhydride and Dimethyl Acetylenedicarboxylate (DMAD) with the Three Isodicyclopentadiene Isomers. Kinetic vs. Thermodynamic Control in Cycloadditions

Paul D. Bartlett* and Chengjiu Wu

*Department of Chemistry, Texas Christian University, Fort Worth, Texas 76129*

The cycloadducts of maleic anhydride and dimethyl acetylenedicarboxylate (DMAD) to the three isodicyclopentadiene isomers have been prepared and studied in terms of competing forward and reverse Diels–Alder reactions and 1,5-sigmatropic rearrangements. At moderate temperature, the maleic anhydride systems are thermodynamically controlled, whereas the DMAD cycloadditions are kinetically controlled. The cycloadduct of DMAD to isomer 3 undergoes a concerted norbornadiene–cycloheptatriene type rearrangement to 14 when heated above 100 °C. Quadricyclane derivatives have been prepared from the DMAD cycloadducts.

Some questions remain unanswered in the cycloaddition studies of the isodicyclopentadiene systems. For example, at elevated temperature where the equilibrium between dienes 1 and 2 is rapid, with most dienophiles only the cycloadducts of 2 are formed.[1,2] Since the amount of 2 in the reaction system is below the detectable limit even at the highest reaction temperature, a steady-state assumption and the knowledge of rates of sigmatropic rearrangement[3-6] of these dienes will lead to an estimate that diene 2 is at least 10⁴ times more reactive than 1. Among the many dienophiles studied, dimethyl acetylenedicarboxylate (DMAD) is the only exceptional case, which, even at high reaction temperature, gives cycloadducts of 1 as the sole product.[1] A thorough examination of these systems thus seems necessary before any final explanation can be given. Because of the higher temperature which is essential for production of 2 from 1, particular attention has been paid to the problem of kinetic vs. thermodynamic control.
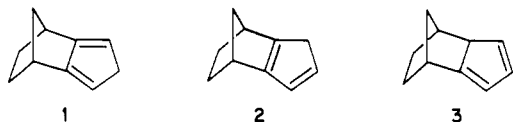
In this paper we report the cycloadducts of maleic anhydride and DMAD to the isomeric isodicyclopentadienes, with observations on the thermal and photochemical conversions of these cycloadducts. We also describe methods for preparing the cycloadducts of DMAD to 2.

Scheme I
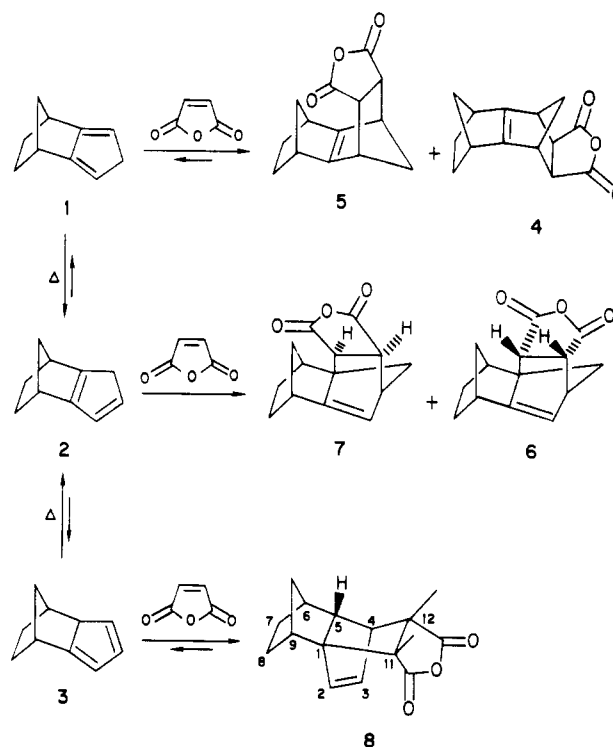
Results

Cycloadditions of Maleic Anhydride. The reactions of maleic anhydride with the three isodicyclopentadiene isomers are summarized in Scheme I. Cycloadditions with isomer 1[7,8] and isomer 2[1] have been reported. Diene 3

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