Highly efficient and selective electrophilic and free radical catalytic bromination reactions of simple aromatic compounds in the presence of reusable zeolites

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Reactions of mono-substituted aromatics of moderate activity with bromine in the presence of stoichiometric amounts of zeolite NaY proceed in high yield and with high selectivity to the corresponding *para*-bromo products. The zeolites can easily be regenerated by heating and reused. Similar *para*-selectivity can be achieved in the case of toluene by use of *tert*-butyl hypobromite as reagent, zeolite HX as catalyst, and a solvent comprising a mixture of tetrachloromethane and diethyl ether. Radical bromination of ethyl 4-methylbenzoate using bromine in the presence of light is catalysed by various zeolites and affords a high yield of ethyl 4-(bromomethyl)benzoate but with no great improvement in selectivity for monobromination.

Introduction

In recent years considerable emphasis has been placed on improvement in the environmental impact of industrial chemical processes.[1] It is well recognised that solids can play a significant role in the development of cleaner technologies through their abilities to act as catalysts, support reagents, entrain by-products, avoid aqueous work-ups and influence product selectivities, and several books on the applications of solids in organic synthesis have appeared.[2] Advances are particularly needed in the area of electrophilic aromatic substitutions,[3] where traditional Lewis acid catalysts are a cause of considerable concern and where reactions are frequently unselective. Bromination, which is of considerable industrial importance, is a case in point.

We have previously developed a highly *para*-selective method for chlorination of toluene and other simple aromatic compounds based on *tert*-butyl hypochlorite and a shape-selective zeolite catalyst.[4,5] Here we report the attempted adaptation of the method, involving *tert*-butyl hypobromite.[6] Although the method is successful for toluene, the reagent is not very stable and the reaction is not suitable for large scale application or application to other substrates.

We have also previously reported a selective bromination method for activated heterocycles based on *N*-bromosuccinimide and silica.[7] However, this method is not successful for bromination of simple aromatic compounds of moderate activity. We have therefore sought to develop an alternative method for *para*-selective bromination of such compounds.

Early attempts to use zeolites to gain regioselective control over bromination of toluene had some success.[8] Limited improvements in selectivity of bromination reactions have also been obtained using clay supported reagents.[9] Recently, however, Sasson and co-workers achieved significant improvements by use of zeolite Y as a catalyst and an epoxide as a hydrogen bromide scavenger.[10,11] They were able to obtain excellent *para*-selectivity (98%) in low yield (*ca.* 10%) or higher yields with
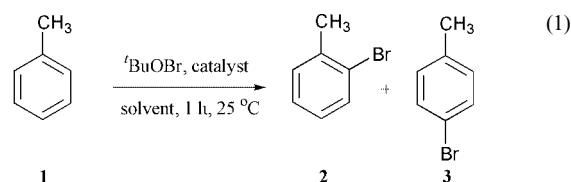
significantly poorer selectivity. These results encouraged us to undertake a detailed study of zeolite catalysed bromination reactions in an attempt to develop highly selective bromination reactions.

In a preliminary communication we reported that bromination of aromatic compounds was highly efficient and *para*-selective when bromine was used as a brominating reagent in the presence of a zeolite.[12] We now also report the full details of this work, as well as results of free radical bromination reactions of ethyl 4-methylbenzoate using bromine in the presence of zeolites and light.

Results and discussion

para-Selective bromination using *tert*-butyl hypobromite

Following our previous success in developing a *para*-selective chlorination reaction for aromatic substrates of moderate reactivity by use of *tert*-butyl hypochlorite as reagent and zeolite HX as catalyst,[4,5] we first attempted the analogous reaction with *tert*-butyl hypobromite as reagent and toluene as substrate. The reagent was prepared as a solution in tetrachloromethane, dichloromethane or petroleum spirit by a slightly modified version of a literature procedure.[13] These solutions, sometimes with diethyl ether added because of the improved *para*-selectivity found with ether as co-solvent in chlorination reactions,[4,5] were allowed to react [eqn. (1)] with

$$
\begin{array}{c}
\text{CH}_3 \\
\text{(1)} \\
\xrightarrow[\text{solvent, 1 h, 25 °C}]{^t\text{BuOBr, catalyst}} \\
\text{CH}_3\text{—Br} \quad + \quad \text{CH}_3\text{—Br}
\end{array}
$$

1   **2**   **3**

an equimolar quantity of toluene in the presence of partially proton exchanged zeolite NaX (13X molecular sieve). The results are shown in Table 1.

From the results in Table 1, it is clear that the reaction is successful in achieving *para*-selective bromination of toluene. The yields were high, but not quantitative. The reactions would

Table 1 Yields and selectivities in HNaX-catalysed reactions according to eqn. (1)[a]

Solvent	Yield (%)[b]	Isomer proportions (2:3)[c]
CH_2Cl_2	85	29:71
20% Et_2O, 80% CH_2Cl_2	77	6:94
CCl_4	92	24:76
20% Et_2O, 80% CCl_4	78	2:98
Petroleum spirit (30–40 °C)	81	19:81
20% Et_2O, 80% petroleum spirit	73	3:97

[a] Bu^{t}OBr (2.6 mmol), toluene (2.5 mmol), solvent (10 ml), zeolite HNaX (1.5 g), 20 °C, 1 h. [b] Absolute yield of monobromotoluenes by quantitative GC. No other toluene-derived products were observed except unreacted toluene. [c] By GC.

Table 2 Yields and selectivities in HNaX-catalysed reactions according to eqn. (1)[a]

% Ether in Et_2O–CCl_4 solvent	Yield (%)[b]	Isomer proportions (2:3)[c]
0	92	24:76
1	63	14:86
2.5	72	8:92
5	75	5:95
10	76	4:96
15	71	3:97
20	70	3:97
25	64	2:98
50	59	1:99
75	49	0:100

[a] Bu^{t}OBr (2.6 mmol), toluene (2.5 mmol), solvent (10 ml), zeolite HNaX (1.5 g), 20 °C, 1 h. [b] Absolute yield of monobromotoluenes by quantitative GC. No other toluene-derived products were observed except unreacted toluene. [c] By GC.

Table 3 Yields and selectivities according to eqn. (1) with different catalysts[a]

| Catalyst	Yield (%)[b]	Isomer proportions (2:3)[c]
None	0	—
Synclyst (13% Al_2O_3)	83	54:46
K10	93	56:44
$MeSO_3H$	92	61:39
HNaX	49	0:100
HNaY	77	36:64
HMordenite	62	54:46
H-ZSM-5	4	30:70

[a] Catalyst (1.5 g), Bu^{t}OBr (2.6 mmol), toluene (2.5 mmol), Et_2O (7.5 ml), CCl_4 (2.5 ml), 20 °C, 1 h. [b,c] As footnotes to Table 1.

require either more time or excess *tert*-butyl hypobromite in order to go to completion. For all solvents tried, selectivities improved when diethyl ether was used as co-solvent. However, invariably the yield also suffered. In an attempt to find the optimum proportion of ether in the solvent mixture, a series of reactions was run in diethyl ether–tetrachloromethane mixtures of different proportions. The results are shown in Table 2.

The results in Table 2 demonstrate that the reaction can be totally *para*-selective, though in modest yield, by use of a solvent mixture consisting of a 3:1 volume ratio of diethyl ether and tetrachloromethane. Leaving this reaction mixture for a longer time did not produce a dramatic increase in yield. We surmise that the low yield is a result of competitive destruction of *tert*-butyl hypobromite in the ether-containing reaction mixture.

For comparison, reactions were also conducted in the absence of any catalyst, with an amorphous solid catalyst (synclyst), with an acid-treated clay (K10), with a solution phase acid (methanesulfonic acid) and with other zeolites (Y, Mordenite and ZSM-5) instead of HNaX. The results are shown in Table 3.

The results in Table 3 demonstrate that an acidic catalyst is required, and that high yields are achievable with catalysts where diffusion is not a problem (synclyst, K10, $MeSO_3H$), but that with such catalysts there is no *para*-selectivity. When diffusion is a significant problem, as for the medium pore zeolite H-ZSM-5, the reaction is slow and the yield is correspondingly low. Mordenite and zeolite Y, which both have large pores, give reasonable yields but with low *para*-selectivity. No other catalyst matches the *para*-selectivity of HNaX, which has large pores to allow reasonable diffusion but weakly acidic sites. This appears to favour a reaction that is sufficiently mild

to allow the shape-selective constraints of the zeolite pores to exert maximum effect.

The low yield over HNaX probably results because the rate of reaction is slow enough to allow effective competition from destruction of the hypobromite in ether. Indeed, when the reaction over HNaX was tried with less active substrates (benzene, ethylbenzene, cumene, *tert*-butylbenzene and bromobenzene), destruction of the hypobromite seemed to become the principle reaction, so that yields of product were very low (0–36%). Consequently, although somewhat better yields could probably be achieved by use of excess reagent, it seemed unlikely that the reaction would be useful as a general method. Therefore, our attention turned to the use of bromine as the reagent.

para-Selective bromination using bromine

Initial reactions were conducted on toluene as substrate and with zeolite HX present as catalyst, but with bromine as reagent [eqn. (2)]. The reaction vessel and the sample collected for analysis were protected from light, to inhibit radical side-chain bromination. Initially, several solvents were tested in order to allow choice of the best solvent for the reaction. The results obtained suggested that dichloromethane was the best solvent of those tried for selective production of *p*-bromotoluene (**3**), at least for reaction in the presence of HX zeolite as catalyst.
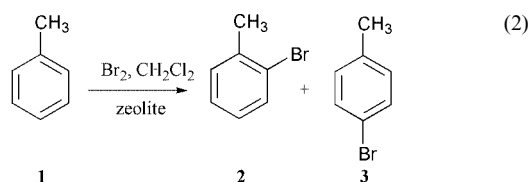
We next investigated the use of various large-pore, proton-form zeolites as catalysts in the reaction of bromine with toluene. Reactions were conducted with a small excess of bromine (1.1 equiv.) at room temperature in dichloromethane as solvent and in the presence of various zeolites. The reaction mixture was stirred and monitored after 1–5 h. The yields of *o*-bromotoluene (**2**) and *p*-bromotoluene (**3**) obtained are shown in Table 4.

The results showed that all zeolites tried were capable of catalysing the reaction to give high yields with fair *para*-selectivities, typically in the region of 80%. The reaction was fastest when HY was used but the *para*-selectivity was somewhat higher when Hβ was the catalyst. The reaction over HY gave 68% yield of *p*-bromotoluene (**3**) within 1 h, which increased to 79% after 3 h. Zeolite Hβ and H-Mordenite gave **3** in yields of 79% and 83%, respectively, after 5 h. This indicated that bromination reactions of toluene over these catalysts were slower but still effective. Clearly, if a proton-form catalyst were to be used for bromination of toluene, then it would be best to

Table 4 Yields according to eqn. (2), over proton-form zeolites[a]

Catalyst	Reaction time/h	Yields (%)[b]		
		1	**2**	**3**
HY	1	16	13	68
HY	2	6	14	75
HY	3	4	15	79
HY	5	2	15	82
HX	1	60	8	30
HX	2	35	16	47
HX	3	21	20	57
HX	5	19	20	61
Hβ	1	43	6	50
Hβ	2	29	7	64
Hβ	3	21	8	71
Hβ	5	12	9	79
HMord	1	51	9	35
HMord	2	24	12	60
HMord	3	12	13	72
HMord	5	1	14	83

[a] Toluene (0.84 mmol), bromine (0.93 mmol), zeolite (0.5 g), in CH_2Cl_2 (6.6 ml), 20 °C. [b] Absolute yields determined by quantitative GC.

Table 5 Yields according to eqn. (2), over Na-form zeolites[a]

Catalyst	Reaction time/h	Yields (%)[b]		
		1	**2**	**3**
NaY	1	5	1	93
NaY	2	5	1	93
NaY	3	5	1	93
NaY	5	5	1	94
NaX	1	8	1	91
NaX	2	7	1	92
NaX	3	6	1	93
NaX	5	6	1	93
Naβ	1	52	5	42
Naβ	2	13	9	77
Naβ	3	7	10	83
Naβ	5	4	10	86
NaMord	1	75	3	20
NaMord	2	54	6	39
NaMord	3	40	7	51
NaMord	5	18	9	71
NaMord	24	3	11	86
NaA	1	98	—	1
NaA	2	95	—	1
NaA	3	94	—	2
NaA	5	93	—	2
NaZSM5	1	75	4	20
NaZSM5	2	60	5	32
NaZSM5	3	58	6	32
NaZSM5	5	56	6	35

[a] Toluene (0.84 mmol), bromine (0.93 mmol), zeolite (0.5 g), in CH_2Cl_2 (6.6 ml), 20 °C. [b] Absolute yields determined by quantitative GC.

Table 6 Yields according to eqn. (2) over different amounts of NaY zeolite[a]

Quantity of NaY/g	Reaction time/h	Yields (%)[b]		
		1	**2**	**3**
0.05	1	75	1	20
0.05	2	73	1	21
0.05	3	72	1	22
0.05	5	70	1	24
0.05	24	50	4	40
0.10	1	44	4	51
0.10	2	38	6	55
0.10	3	32	8	60
0.10	5	22	10	67
0.10	24	—	15	84
0.25	1	14	2	82
0.25	2	11	2	82
0.25	3	11	2	82
0.25	5	11	2	84
0.25	24	10	3	85
0.50	1	5	1	93
0.50	2	5	1	93
0.50	3	5	1	93
0.50	5	5	1	94
0.55	1	—	1	98
0.55	2	—	1	98
0.55	3	—	1	98
0.55	5	—	1	98
0.55	24	—	1	98

[a] Toluene (0.84 mmol), bromine (0.93 mmol), zeolite NaY, in CH_2Cl_2, 20 °C. [b] Absolute yields determined by quantitative GC.

leave the reaction longer than one hour in order to obtain a high yield.

The results with HY and HX, which have the same gross crystalline structure, showed that zeolite Y gave a higher yield and better selectivity than zeolite X. This is presumably due to differences in the number and strengths of the acid sites and therefore in the overall acidity/basicity of the solid. Therefore, further experiments were carried out using Na-exchanged zeolites in order to investigate further the effect of the basicity of the zeolite used.

Some of Sasson's best selectivities were achieved using NaY zeolite [10,11] so we next investigated the sodium forms of a range of zeolites. Reactions were conducted in the same way as those using proton-form zeolites. The sodium forms of zeolite A and ZSM-5 were also included, in order to provide comparison with a small pore and a medium pore zeolite. The results obtained are recorded in Table 5.

It is clear from Table 5 that the yields of brominated toluenes **2** and **3** formed were broadly a function of the size of the pores. Thus, almost no reaction took place when the small pore zeolite A was used. Reaction took place to a modest extent with the medium pore Na-ZSM-5 and also with the larger pore Mordenite, which has linear channels. The other large pore zeolites, which have three dimensional pore systems, catalysed the reaction to a greater extent. This was particularly true of the X and Y zeolites, where reaction was almost complete, even after 1 h.
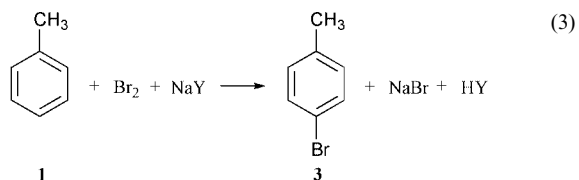
Zeolite Naβ gave a better yield of *p*-bromotoluene (**3**), with higher selectivity, than zeolite Hβ. To our surprise, NaY and NaX produced high yields of almost entirely 4-bromotoluene (**3**), in contrast to the results of Sasson.[10,11] Furthermore, the reactions using NaY and NaX were fast, giving high yields of bromotoluenes by the time the reactions were first monitored after 1 h at 20 °C. The rates of reactions with the other zeolites were lower, giving lower yields of brominated products even after 5 h. Nevertheless, the yield with Naβ was 86% after 5 h and that with Na-Mordenite crept up to 86% after 24 h.

The relative reaction rates can again be understood in terms of the pore structures of the zeolites. The large cavities created by the interconnecting channels of NaY and NaX, and to a lesser extent Naβ, allow readier diffusion of the reactants to the active sites. By contrast, NaA fails to react because the pores are too small for toluene to enter. However, it was not immediately obvious why NaY and NaX should induce reactions at faster rates than their proton counterparts, nor why the yields and selectivities should be so much higher than those reported by Sasson.[10,11]

The major difference between our experiments and corresponding ones carried out by Sasson was in the quantity of zeolite used. We therefore investigated the effects of variation in the amount of zeolite NaY used. The results obtained are recorded in Table 6.

As the results in Table 6 show, there is a strong dependency of the yield on the quantity of NaY used and the reaction became quantitative when 0.55 g was employed. The reaction was

slower and produced a low yield when the quantity of the catalyst was only 0.05 g, broadly in line with the observations of Sasson.[10,11] These results are consistent with the occurrence of a rapid and stoichiometric reaction involving the NaY zeolite [eqn. (3)] competing favourably with a slower and less selective

$$\text{CH}_3\text{-C}_6\text{H}_5 + \text{Br}_2 + \text{NaY} \longrightarrow \text{4-Br-C}_6\text{H}_4\text{-CH}_3 + \text{NaBr} + \text{HY} \quad (3)$$


1   **3**

catalytic reaction involving the HY zeolite (compare Table 4). When such trends were seen before, the results were interpreted in terms of a catalytic process that was damaged by the presence of HBr.[8,10,11]

Zeolite X has the same crystalline structure as zeolite Y but the Si:Al ratio is lower (*i.e.* it contains a higher proportion of Al). The number of anionic sites on the lattice is related to the number of Al atoms and the number of exchangeable sodium atoms in NaX or NaY is related to the number of anionic sites. Therefore, NaX was used instead of NaY to see the effect of changing the quantity of this catalyst. The results obtained are recorded in Table 7.

As can be seen from Table 7, the same effect was observed when NaX was used as the catalyst as when NaY was used. The yield of **3** depended on the quantity of NaX used in the bromination reaction. The *para*-regioselectivity was high in all cases. The only differences between NaX and NaY were in the reaction rate and in the amount of product formed by the initial reaction. Surprisingly, it was NaY rather than NaX that resulted in the more rapid and higher yielding reaction, despite the greater quantity of exchangeable sodium ions in the latter. The explanation for this is not yet clear, but may be connected with constraints to diffusion and with accessibility of sites in the zeolite with the greater initial concentration of sodium cations, especially as the quantity of NaBr deposited in the pores builds up.

Although the best conditions allow the quantitative formation of 4-bromotoluene (**3**) with very high selectivity, it is unattractive for large-scale use to require 3.8 times as much NaY as the mass of product formed. This would be less of a problem if the solid could be easily regenerated following removal of the bromotoluene. It appears from eqn. (3) that the spent solid should have finely dispersed sodium bromide in the pores of HY zeolite. Simple heating of the solid might therefore cause expulsion of gaseous hydrogen bromide and regeneration of NaY [eqn. (4)]. Alternatively, a standard ion-exchange

$$\text{NaBr} + \text{HY} \xrightarrow{\text{heat}} \text{NaY} \cdot \text{HBr} \quad (4)$$
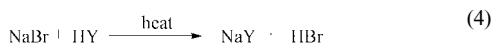
process involving reflux of the spent zeolite with aqueous NaBr should effect its conversion back into its sodium form.

Calcination of the solid at 400 °C did indeed completely regenerate its reactivity. The regenerated material gave the same yield and selectivity as the original NaY. Therefore, in practice it should become possible to produce much larger quantities of 4-bromotoluene from a particular batch of solid by repeated regeneration and reuse.

The amount of solvent might also affect the yield and *para*-selectivity of the reaction. Therefore, a series of experiments was conducted in which different amounts of solvent were used. The results obtained are recorded in Table 8.

The results showed that the quantity of dichloromethane could be reduced without detriment until there was insufficient to keep the reaction mobile. Decreasing the amount of solvent made the reaction more concentrated but the toluene was

Table 7 Yields according to eqn. (2) over different amounts of NaX zeolite[a]

Quantity of NaX/g	Reaction time/h	Yields (%)[b]		
		1	2	3
0.10	1	68	1	30
0.10	2	64	2	33
0.10	3	63	2	33
0.10	5	61	2	36
0.10	24	47	4	49
0.20	1	41	2	54
0.20	2	36	4	59
0.20	3	32	5	62
0.20	5	26	6	65
0.20	24	12	8	79
0.50	1	8	1	91
0.50	2	7	1	92
0.50	3	6	1	93
0.50	5	6	1	93
0.50	24	6	1	93
0.55	1	4	1	93
0.55	2	1	1	96
0.55	3	1	1	96
0.55	5	1	1	96
0.55	24	—	1	97

[a] Toluene (0.84 mmol), bromine (0.93 mmol), zeolite NaX, in CH_2Cl_2 (6.6 ml), 20 °C. [b] Absolute yields determined by quantitative GC.

Table 8 Yields according to eqn. (2), with different quantities of solvent[a]

CH_2Cl_2/ml	Yields (%)[b]		
	1	2	3
0[c]	—	20	79
2	—	1	95
3	—	1	97
5	5	1	93

[a] Toluene (0.84 mmol), bromine (0.93 mmol), zeolite NaX (0.5 g), in CH_2Cl_2, 20 °C. [b] Absolute yields determined by quantitative GC. [c] Toluene (5 ml) was used as its own solvent and calculation done with respect to the amount of bromine added.

still converted with high selectivity into 4-bromotoluene (**3**) when the amount of solvent was reduced to 2 ml. The *para*-regioselectivity was much lower when toluene was used as its own solvent, while with no solvent at all the mixture could not be stirred. The solvent probably aids diffusion into the zeolite pores by increasing the mobility of the system. However, in an industrial situation it might be important economically to avoid a solvent separation step. This would be possible if 4-bromotoluene could be utilised as the solvent. Therefore, an experiment was conducted in 4-bromotoluene as solvent. Indeed, 4-bromotoluene could be used successfully as a solvent instead of dichloromethane, with no diminution in yield or selectivity. Consequently, this approach now becomes a commercially realistic possibility for the synthesis of 4-bromotoluene (**3**).

In order to demonstrate that the reaction was applicable on a preparative scale, a single reaction was conducted on a 76 mmol scale (using 7.0 g of toluene). The reaction produced a product (12.5 g, corresponding to a 96% yield if all **3**), the ^{1}H NMR spectrum of which indicated that it was about 96% pure. A single distillation without fractionation produced a liquid forerun (0.27 g), which was mainly **3** together with small quantities of solvent and other impurities, a solid main fraction (10.35 g, 80% yield) that was essentially pure **3** (mp 26–28 °C), and a dark residue (1.35 g), which still contained substantial quantities of **3**. It is clear that with optimisation of the reaction procedure for larger scale work and a more

Table 9 Yields according to eqn. (5)[a]

R of substituted benzenes 4	Yields (%)[b]		
	4	5	6
H	6	—	91[c]
Me	—	1	98
Et	—	1	97
i-Pr	—	—	98
t-Bu	2	—	97[d]
F	8 (6)[e]	—	92 (93)[e]
Cl	22 (17)[e]	—	78 (82)[e]
Br	44 (34)[e]	—	56 (66)[e]
MeO	—	—	93

[a] Substrate (0.84 mmol), bromine (0.93 mmol), zeolite NaY (0.55 g), in CH₂Cl₂ (*ca.* 8 ml), 20 °C, 5 h. [b] Absolute yields determined by quantitative GC. [c] 2% of dibromo product also obtained. [d] *ca.* 1% of a side product also obtained. [e] Figures in parentheses are for similar reactions, but with 0.8 g of NaY.

sophisticated distillation process the reaction would produce a very high isolated yield of extremely pure material, which is impossible by any previous procedure.

In order to explore the scope of the reaction, similar conditions (small scale) were applied to a range of substituted benzenes **4** according to eqn. (5). The yields of brominated products **5** and **6** obtained are recorded in Table 9.

(5)
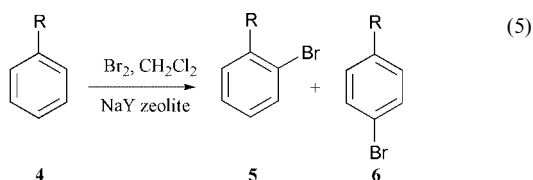
As Table 9 shows, the reaction gives high yields and *para*-selectivities for a range of substituted benzenes **4** of moderate activity, including alkyl and halogenobenzenes.

Several features of these reactions are noteworthy. First, the sodium forms of the zeolites generate much faster reactions than the proton forms. This has been noted before,[8,10,11] but despite this fact, the common view has been that increasing the Brønsted acidity of the active sites enhances the activity. Such an inference appears to be unsustainable, and the somewhat lesser activity of NaX than NaY may be due to greater diffusion constraints or some other factor, rather than to the lower acidity of the corresponding proton-form zeolite.

Second, the selectivity is remarkable, almost exclusive formation of the *para*-isomer being achieved in all cases. In the many prior studies of zeolite-induced aromatic bromination reactions (see refs. 8, 10, 11 and citations therein) selectivities at total conversion were significantly less, especially for toluene. Also, conventional wisdom would maintain that space within the pores of zeolite Y is so abundant that there is little opportunity for significant shape-selectivity. Yet the results defy this argument. It appears to be important that the reaction requires the substrate, the bromine and the sodium form of the zeolite all to be involved in the process. Perhaps even the presence of solvent molecules plays a role. In this case, the space within the pores could become much more congested than might be envisaged in a cursory consideration, and this might lead to the observed selectivity.

We consider two potential mechanisms that might be involved in the process occurring within the pores. One would require a three-body process involving adsorption of both the substrate and the bromine on the internal surface of the zeolite and in close proximity to each other. The reaction could then take place between bromine and the substrate, with assistance to polarisation of the bromine molecule coming from the

sodium cation, and assistance for removal of the proton from the aromatic ring coming from the zeolite framework. This would lead directly to NaBr and HY as well as to the organic product.

The alternative would involve initial reaction between the zeolite and bromine to give a surface hypobromite species, which would become the active brominating agent. An aluminium site with Lewis-acid properties would be generated simultaneously [eqn. (6)]. The surface hypobromite site, with

(6)
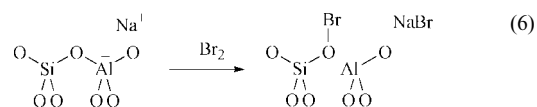
NaBr deposited alongside it, might be rather inaccessible to the more hindered *ortho*-position of the substrate. This would enhance the tendency, already seen with *tert*-butyl hypobromite, for *para*-preference in these reactions, thereby allowing the extreme selectivity observed. This latter mechanism bears some similarity to one proposed previously by Russian workers.[14]

Side-chain bromination

Having achieved selective nuclear bromination of substituted benzenes, we next turned our attention to the possibility of selective side-chain bromination. We chose ethyl 4-methyl-benzoate (**7**) as substrate because the ester group would lower reactivity towards nuclear substitution and because the product, ethyl 4-(bromomethyl)benzoate (**8**), could be of commercial interest.

Ethyl 4-(bromomethyl)benzoate can be obtained from the reaction of 4-bromomethylbenzoyl chloride or bromide with ethanol.[15] Whilst such a method can be quite efficient, it suffers from the poor availability and stability of acid halides, which considerably limits its scope, while direct reaction between the carboxylic acid and ethanol is prone to competitive displacement of bromide by ethanol. An alternative approach involves bromination of ethyl 4-methylbenzoate (**7**) using *N*-bromo-succinimide (NBS),[16,17] but NBS as a brominating reagent is relatively expensive compared to bromine. The NBS reaction also produces significant quantities of ethyl 4-(dibromomethyl)-benzoate (**9**) as a by-product and requires separation of succinimide from the product. It was therefore of interest to see if zeolites could be used to catalyse and to control the direct reaction of **7** with bromine. This should offer the advantages of a cheap reagent, easy separation of the zeolite from the reaction mixture by filtration, possible reuse of the catalyst, and an environmentally friendly process.

As a test case, the reaction of ethyl 4-methylbenzoate (**7**) was conducted with excess bromine (1.33 mole equivalents) in dry dichloromethane without zeolite [eqn. (7)].

(7)
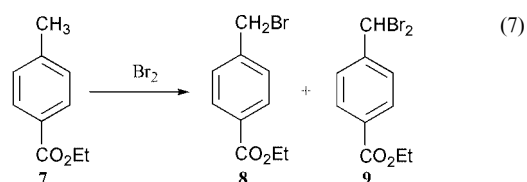
A solution of bromine in dichloromethane was added in a dropwise manner to a stirred solution of **7** in dichloromethane over 20 min. The reaction mixture was then stirred at room temperature for 2 h. After quenching and work-up, ethyl 4-(bromomethyl)benzoate (**8**) was obtained in 42% yield as determined by the use of ¹H NMR spectroscopy. Ethyl 4-(dibromomethyl)benzoate (**9**), presumably formed by reaction of **8** with further bromine, was also obtained, in 0.5% yield. Moreover, analysis of the reaction mixture showed that 57% of the starting material remained unreacted.

Table 10 Yields according to eqn. (7)

Br$_2$ (equiv.)	Solvent	Reaction time/h	Reaction temperature/°C	Yields (%)[a]		
				7	8	9
1.33[b]	CH$_2$Cl$_2$	2	20	57	42	0.5
1.33[c]	CH$_2$Cl$_2$	2	20	57	42	0.5
1.33	CH$_2$Cl$_2$	2	20	57	42	0.5
1.33	CH$_2$Cl$_2$	4	20	42	57	1
1.33	CH$_2$Cl$_2$	6	20	32	65	2
1.33	CH$_2$Cl$_2$	7	20	33	65	2
1.43	CH$_2$Cl$_2$	4	20	42	57	1
1.02[d]	CH$_2$Cl$_2$	3	20	96	4	—
1.02	CH$_2$Cl$_2$	1	42 (reflux)	8	82	10
1.23	CH$_2$Cl$_2$	1.5	42 (reflux)	5	82	13
1.07	CH$_2$Cl$_2$	2	42 (reflux)	8	82	9
1.02	MeOH	3	20	97	3	—
1.02	CH$_3$CN	3	20	96	14	—
1.02	CHCl$_3$	3	20	17	77	6

[a] Yields were determined by ^{1}H NMR spectroscopy. [b] Dry dichloromethane (DCM) was used and bromine was added dropwise. [c] Dry DCM was used. [d] Reaction carried out in the dark.

A series of experiments was conducted in which different solvents were used and the conditions of the reaction were varied in an attempt to improve the yield of the desired product **8** and to eliminate the formation of the side product **9**. The results obtained are recorded in Table 10.

It was found that dropwise addition of bromine and dry conditions were not necessary. Not surprisingly, the yield of **8** was improved (to 82%) when a mixture of **7** and bromine (1.07 equiv.) in dichloromethane was held under reflux for 2 h. However, the side product **9** was obtained in a yield of about 9% under such conditions. It was also found that dichloromethane and chloroform are the best solvents of those tried in which to conduct the bromination reaction. The room temperature reaction took place faster in chloroform, in which the monobromo derivative **8** was obtained in 77% yield, but there was a relatively high yield (*ca.* 6%) of the dibromo derivative **9**. Very low yields of the desired product **8** were obtained when methanol or acetonitrile was used as solvent.

The yield of **8** was only *ca.* 4% when the bromination reaction was carried out in dichloromethane in the dark, verifying the radical nature of the process. As can be seen from Table 10, the yield of the side product **9** could be as high as 13%. This shows that the reaction between **8** and further bromine is quite rapid under the reaction conditions tried.

Our attention was turned next to the use of various types of zeolite (5A, 4A, 3A, 13X, NaM, HY and Hβ) to catalyse and/or control the bromination process in different solvents. When a mixture of **7** (6.10 mmol), bromine (6.22 mmol) and zeolite 5A (2.0 g) in dichloromethane was stirred for 3 h at room temperature, the yield of **8** was 83% and the side product **9** was obtained in a yield of *ca.* 7%. Similar results were obtained when a smaller amount of 5A (1.0 g or even 0.1 g) was used as a catalyst. It had been hoped that slow release of bromine from within the zeolite pores might help enhance the selectivity, but the effect was not large if it was valid at all.

The results with other zeolites are shown in Table 11. Again, when the reaction was carried out in methanol or acetonitrile as solvent, or in the dark, very low yields of **8** were obtained. The zeolites and solvent were varied in order to try to eliminate the side product, but none of the conditions were completely successful in this respect (Table 11).

As can be seen from Table 11, the yield of **8** could be improved up to 84%, but the yield of **9** was always significant also. The use of zeolites enhanced the rate of the bromination process of ethyl 4-methylbenzoate (**7**) and improved the yield of the desired product, but none of the zeolites brought about substantial improvement over the selectivity of the reaction.

Conclusion

The reaction of bromine with substituted benzenes of moderate activity in the presence of sufficient NaY zeolite at room temperature provides a convenient, high yielding and highly regioselective method for synthesis of *para*-brominated products. Furthermore, heating easily regenerates the zeolite and the reaction works almost as well on a vastly larger scale even without any modification to the conditions. Consequently, this approach becomes a commercially realistic possibility for the synthesis of *para*-bromo substituted benzenes.

High *para*-selectivity can also be achieved in bromination of toluene by use of *tert*-butyl hypobromite as reagent, HNaX zeolite as catalyst, and a solvent mixture comprising diethyl ether and tetrachloromethane, but the reaction is not general. The use of zeolites also enhances the rate of light-induced side-chain bromination of ethyl 4-methylbenzoate, but does not substantially diminish the tendency to over-bromination.

Experimental

A PU 4400 Gas Chromatograph (Philips) fitted with a capillary column RTX-1 (100% polydimethylsiloxane, 0.32 mm ID) was used to analyse reaction mixtures in the case of the nuclear bromination reactions. Temperature programmed heating between 70 °C and 200 °C was employed and decane or undecane was added as an internal standard to allow quantification. NMR was used for quantification in the case of side-chain bromination reactions. ^{1}H NMR spectra were recorded on a Bruker, AC 400 spectrometer operating at 400 MHz. Assignments of signals are based on coupling patterns and expected chemical shift values.

Zeolites

Commercial zeolites were purchased from Aldrich Chemical Company (3A, 4A, 5A, 13X, NaY catalyst support) or provided as gifts by Zeolyst International. Ion-exchanged forms were obtained by heating the commercial sodium or proton forms at reflux with a 1 M solution of the appropriate halide salt, followed by washing with water until the washings were halide-free and then calcination at 450 °C. Proton forms were obtained by initial formation of the corresponding ammonium forms, which break down to the proton forms during calcination.

Bromination reactions

Bromination of toluene with *tert*-butyl hypobromite. In an oven-dried, 50 ml round-bottomed flask were placed zeolite

Table 11 Yields according to eqn. (7) in the presence of various zeolites[a]

Zeolite	Mass used/g	Solvent	Yields (%)[b]		
			7	8	9
5A	0.1	CH_2Cl_2	10 (17)[c]	82 (77)[c]	8 (6)[c]
5A	0.5	CH_2Cl_2	10	82	8
5A	1.0	CH_2Cl_2	5	83	10
5A	1.0[d]	CH_2Cl_2	10	82	7
5A	1.0[e]	CH_2Cl_2	96	4	—
5A	1.0	MeOH	98	2	—
5A	1.0	MeCN	87	13	—
5A	1.0	$CHCl_3$	20	69	19
5A	2.0	CH_2Cl_2	10	83	7
4A	0.1	CH_2Cl_2	7	81	12
4A	1.0	CH_2Cl_2	6	81	12
3A	0.1	CH_2Cl_2	9	78	13
3A	0.5	CH_2Cl_2	2	84	14
3A	1.0	CH_2Cl_2	11	80	9
13X	0.1	CH_2Cl_2	9	82	9
13X	0.5	CH_2Cl_2	8	81	11
13X	1.0	CH_2Cl_2	15	61	24
NaMord	0.1	CH_2Cl_2	14	80	6
NaMord	0.5	CH_2Cl_2	3	82	14
NaMord	1.0	CH_2Cl_2	8	83	8
HY	0.1	CH_2Cl_2	9	83	7
HY	0.5	CH_2Cl_2	9	83	7
HY	1.0	CH_2Cl_2	4	83	12
Hβ	0.1	CH_2Cl_2	47	51	1
Hβ	0.5	CH_2Cl_2	15	80	5

[a] Compound **7** (6.1 mmol), bromine (6.22 mmol), zeolite, solvent, 20 °C. [b] Yields were determined by ^1H NMR spectroscopy. [c] Figures in parentheses are for a similar reaction but under reflux for 1 h. [d] Bromine was loaded into the zeolite. [e] Reaction carried out in the dark.

(1.50 g) and a magnetic follower. A standard solution containing toluene (2.50 mmol) and undecane (1.25 mmol, internal standard), in the appropriate solvent (7.4 ml), was added, followed by a solution of *tert*-butyl hypobromite in the same solvent (1.00 M as estimated by iodometric titration, 2.60 ml, 2.6 mmol). The flask was stoppered and the mixture was stirred for 1 h at ambient temperature. The mixture (or a sample of it) was filtered through a glass sinter (P3) and the zeolite was washed with a little extra solvent. The solution was analysed by GC (see Tables 1–3).

Bromination of substituted benzenes 4 with bromine. A sample of a calcined catalyst (0.05–0.55 g) was placed in a 25 ml round-bottom flask with dichloromethane (5 ml). A solution of **4** (~0.70 ml of 10% solution in dichloromethane, 0.84 mmol) and decane as a standard (0.43 ml of 10% solution in dichloromethane, 0.039 g) was then added. The mixture was protected totally from light, and stirred for a few minutes. Bromine (0.48 ml of 10% solution in dichloromethane, 0.93 mmol) was then added dropwise with rapid stirring in the dark. At various times samples were taken (also protected from light) from the reaction mixture and were analysed by GC.

Preparative scale bromination of toluene. Catalyst NaY (55.112 g, Aldrich 33,444-8, calcined at 550 °C for 24 h) was added to dichloromethane (400 ml) in a 1 l round-bottomed flask. To the mixture, a solution of toluene (7.011 g, 76.2 mmol) in dichloromethane (100 ml) was added. The mixture was stirred in the dark for 15 min and bromine (13.783 g, 86.1 mmol) in dichloromethane (100 ml) was then added dropwise with rapid stirring over 45 min in the dark. The mixture was stirred at room temperature for 5 h in the dark and then filtered. The solid was washed with dichloromethane (3 × 100 ml) and the washings were combined with the filtrate. The combined solution was evaporated on a rotary evaporator at 20 °C to give a pale yellow liquid (12.09 g, 93%). The zeolite was further washed with acetone (2 × 100 ml) and the washings were evaporated to give a brown liquid (0.40 g). The two parts of the

product were combined and distilled at atmospheric pressure. A forerun was collected up to 140 °C (uncalibrated thermometer) and the product was then collected until the temperature dropped again to 130 °C. The product (10.35 g, 80%) solidified on cooling to yield an off-white solid, mp 26–28 °C (lit.[18] 26–29 °C). A brown residue (1.35 g) remained in the distillation flask. Both the forerun and the residue contained a substantial proportion of 4-bromotoluene, as shown by NMR, while the main fraction was essentially the pure product.

Bromination of ethyl 4-methylbenzoate (7). A mixture of ethyl 4-methylbenzoate (1.0 g, 6.10 mmol), zeolite (0.1–2.0 g) and bromine (0.32 ml, 6.22 mmol) in dichloromethane (20 ml) was stirred at room temperature for a period of time. The reaction was stopped by the addition of a dilute aqueous sodium sulfite solution (5 ml). The reaction mixture was filtered and the zeolite was washed with dichloromethane (2 × 5 ml). The organic layer was separated, washed with water (2 × 10 ml), dried ($MgSO_4$), and evaporated to dryness under reduced pressure. The residue obtained was submitted for ^1H NMR spectroscopy.

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