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Heightened Selectivity in Aromatic Nitrations and Chlorinations by the Use of Solid Supports and Catalysts

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Introduction

Most organic chemists regard electrophilic aromatic substitution as a closed book. Interpretation is one of the major triumphs of mechanistic theory, and few want to question that understanding. Nevertheless, there are still gaps and inconsistencies in our comprehension. Also, many practical problems remain unsolved. For example, the commercial production of *p*-nitrotoluene in the United Kingdom alone runs to some 30 000 T per year. The poor selectivity of the reaction means that this highly desirable product is accompanied by 60 000 T of less desirable *o*-nitrotoluene. Until quite recently the ortho isomer represented a valueless waste product. At times it was even burned to provide heat for the plant. Environmental considerations nowadays would not allow such a means of disposal, and large amounts of unwanted byproducts in general represent

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major problems. Clearly, there is a need for more regioselective control of electrophilic aromatic substitution. This Account describes our efforts involving the use of solid supports and catalysts in the fields of nitration and chlorination of aromatic compounds.

Assets of Solid Supports and Catalysts. Traditionally, solids, especially chromatographic adsorbents, have been used in reactions to provide a surface on which to spread out a reagent. Empirically, such procedures were often found to provide high yields under mild conditions. The ease of setup and workup often was matched only by the cleanliness of the reactions.¹ However, little thought appeared to go into the choice of the solid, except to make sure that it offered ample active surface. Progress in surface science,² the improved understanding of heterogeneous catalysis, and the availability of numerous new solids now provide opportunities for better design of catalysts which can lead to enhanced performance in the attendant processes.

Microporous solids such as silica, alumina, and aluminosilicates offer a wide range of active sites for catalysis (e.g., acidic or basic sites³) and most often can be regenerated if deactivated during a reaction. Furthermore, they bring other assets. Constraining an organic molecule onto a solid surface has interesting consequences. The adsorbate undergoes reduction in dimensionality, from a three-dimensional reaction volume to a surface. Thereby the frequency of diffusional encounters increases and along with it the preexponential term in the kinetic (Smoluchowski–

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Debye) equations.^{4,5} The adsorbates also migrate to catalytic sites with an attendant electronic redistribution,⁶ hence creating a reduction in the activation energy. The geometric consequence of anchoring onto a solid is to restrict the angles of attack, i.e., to enhance selectivity. Further increases in selectivity stem from molecular sieving by microporous solids such as zeolites, which have smooth inner walls with high diffusivities, and can lead to shape selectivity.¹

Nitration

Reagents for Nitration: The Active Species.

Sulfonitric mixtures have been used successfully for 150 years in industrial nitration processes.^{7,8} The role of sulfuric acid is to turn nitric acid into the kinetically significant species, the nitronium ion, NO_2^+ . Spurred by the belief in greater activity and selectivity of a naked nitronium ion, many authors have sought its incorporation in an ion pair having a highly stabilized anion. Thus, acetyl nitrate, AcONO_2 , has been used in this guise since the early 1960s.⁹ Likewise, benzoyl nitrate, BzONO_2 ,^{10,11} and triflic nitrate, TfONO_2 ,¹² have served as nitronium delivery systems, as have nitronium salts such as tetrafluoroborate and hexafluorophosphate, and transfer reagents derived from them.¹³

Dinitrogen tetroxide, N_2O_4 , is the dimer of NO_2^* radicals, a convenient form for their storage and release. Other heterolytic modes for its dissociation are into nitrite and nitronium ions; and into nitrate and nitrosonium, NO^+ , ions.¹⁴ Accordingly, N_2O_4 has been widely used for aromatic nitrations. Sometimes, it is impregnated on inorganic solids such as alumina and silica. In the former case, calculations and spectral data point to transformation of alcohol surface groups into unidentate nitrate active species, $\text{O}_5\text{Al-ONO}_2$.¹⁵

The classical Hughes–Ingold mechanism for aromatic substitution is a two-step sequence. The Wheland intermediate formed in the first step deprotonates to the final product in the second step.¹⁶ This simple

description was enlarged to make room for additional reaction steps. Thus, Kenner proposed transfer of a single π electron from the aromatic substrate to the electrophile, as the initial step.¹⁷ Nagakura showed operation of a strong driving force for such single electron transfer (SET) whenever the electron affinity of the electrophile exceeds the ionization potential of the aromatic.¹⁸ Brown later postulated the intervention of charge-transfer complexes as intermediates.¹⁹ Perrin championed an initial SET between the aromatic donor and the nitronium or nitrosonium ion acceptors to form an ion radical pair, $[\text{ArH}^{+\bullet}, \text{NO}_2^*]$ or $[\text{ArH}^{+\bullet}, \text{NO}^*]$, which collapses in a fast step to the Wheland intermediate.²⁰ Accordingly, nitration occurs preferentially at the sites of the $\text{ArH}^{+\bullet}$ radical cation with the greatest potential for new bond formation.²¹ Since collapse of a radical pair is involved, positions with the greatest unpaired spin density will be attacked preferentially. The observed isomer distributions for the reaction products thus preserve the memory of a transient electronic structure. They reflect spin delocalization in the radical cationic intermediate. This assumes its irreversible collapse into the Wheland intermediate.

To summarize and simplify the mechanistic picture currently valid for nitronium ion aromatic nitrations, the two limiting mechanisms are (i) the classical two-step mechanism as taught worldwide to undergraduates and (ii) a multistep mechanism, proceeding through the $\text{ArH}^{+\bullet}$ radical cation trapping an NO_2^* (or an NO^*) radical before collapsing to the Wheland intermediate. Both these mechanistic extremes share the (fast) last step, viz., deprotonation of the Wheland intermediate into the final reaction product.

Nitration of Phenols. A survey of the literature shows nitration of phenol to lack positional selectivity entirely! The process follows statistics with ca. 67% ortho and 33% para nitration. Thus, the challenge, if *p*-nitrophenol is the desired product, is to reverse the distribution into predominant para preference. As mentioned above, the classical Hughes–Ingold (ionic) and Perrin (radical) pathways compete. The latter gives a product distribution stemming from the unpaired spin density in the radical cation intermediate. This unpaired spin density is greater in the para than in the ortho position.²² Hence, the logical way to a para preference is to make the reaction opt for the radical instead of the ionic pathway. To guide the system along this route, the Liège group has devised a rather efficient heterogeneous nitration procedure. The main ingredient is “clayfen”, i.e., montmorillonite clay (K10) supported ferric nitrate.²³ The clay, the ferric ions with which it is doped, and the nitrosonium ions that it evolves are all oxidants cooperating to preoxidize the phenol into the corresponding radical cation. The results display significant improvements in yields and selectivity with respect to earlier procedures.²⁴ An illustration is estrone. The yield in the pharmaceuti-

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Table I. Influence of a Clay Support on the Regioselectivities in the Nitration of Various Alkylbenzenes

| substrate | product distribution (o,m,p) | |
|---------------------------|---|--|
| | heterogeneous ^a ("claycop" + Ac ₂ O) | homogeneous ^b (HNO ₃ + Ac ₂ O) |
| toluene | (43,2,55) | (63,3,34) |
| ethylbenzene | (27,3,70) | (48,5,47) |
| <i>n</i> -propylbenzene | (28,3,69) | (47,5,48) |
| isopropylbenzene | (14,3,83) | (24,8,68) |
| <i>n</i> -butylbenzene | (34,2,64) | (48,5,47) |
| <i>tert</i> -butylbenzene | (8,6,86) | (11,12,77) |

^a Reference 31. ^b Baas, J. M. A.; Webster, B. M. *Recl. Trav. Chim. Pays-Bas* 1971, 90, 1081–1088, 1089–1097; 1972, 91, 517–527.

cally significant 2-nitro derivative increases from the then very recent literature record of 35–40%²⁵ to 55%, and at much reduced cost.²⁶

Recently, Poirier and Vottero²⁷ examined systematically the ability of commercial, hydrated nitrates in mononitration of phenols. The nature of the metal was determinant. Some were inactive: Co(II), Ni(II), Zn(II). The convenient and inexpensive iron(III) nitrate gave 50% ortho and 50% para nitration of phenol. Chromium(III) nitrate increased the para preference to 76%, in another quantitative reaction. Conversely, copper(II) nitrate gave exclusive (52%) ortho formation in one experiment (which we tried unsuccessfully to reproduce: in our hands, two different tries gave overall yields in mononitro products of 37% and 47%, with 14/24 and 10/37 ortho/para distributions, and substantial formation of polynitrated products²⁸). Other conditions led Poirier and Vottero to the usual ortho preference (47/32 in one case; 50/29 in another). With Fe(III) nitrate, the yield in 2-nitroestrone was 79%.

Nitration of Toluene and Other Normally Activated Hydrocarbons. As mentioned in the Introduction, toluene nitration has considerable industrial importance: an economic significance matched only by its centrality to mechanistic discussions.

In general, alkylbenzenes are nitrated ca. 50% ortho and 50% para.^{7,8} It behooves modern investigators armed with active surfaces to boost the para selectivity. A convenient start is the radical cationic pathway. Thus, comparison of the unpaired electron densities in the toluene radical cation, i.e., 1/3 (ipso), 1/12 (ortho), 1/12 (meta), and 1/3 (para), indicates the latter position as the favored site of attack by the NO[•] (or NO₂[•]) radical. Of course, the analysis is in its general lines pertinent to the other alkylbenzenes as well. Indeed, experimental results bear out the prediction of a high para preference for reactions in which the radical pathway is expected to predominate (Table I). These stem from use of montmorillonite clay supported cupric nitrate ("claycop"²⁹) in the presence of acetic anhydride (Menke conditions³⁰) to mop up excess humidity; the substrate for convenience serves as its own solvent; the

reaction is run under very mild conditions, for 2 h at room temperature, and isolated yields are in the range 75–98%.³¹

Is there a role of the montmorillonite K10 clay in favoring the radical cation pathway, held responsible for these regioselectivities? The answer is "yes" from the comparison with results under classical homogeneous conditions (Table I). A "hard"³² metallic nitrate is called for, so that the ion–molecule encounter (that of NO⁺ or NO₂⁺ with the aromatic), stabilized by ca. 10 kcal·mol⁻¹,³³ that precedes the electron transfer be charge-controlled. This expectation is borne out by the observations: the yields after 24 h are 97% and 100% with the hard Cu²⁺ and Zn²⁺ cations, respectively; Ce³⁺ (70%) is a hard cation, whereas Hg²⁺ (19%) is a softer ion.³⁴ The nature of the solvent has a slight influence on the regioselectivity. Whereas with fluorocarbon FC-72 (a mixture of C₆F₁₄ isomers) and with acetonitrile no reaction occurs, the para selectivity is less than 50% in cyclohexane, acetone, bromochloromethane, 1,2-dichloroethane, and 1,1,2,2-tetrachloroethane. It remains below 55% in *n*-hexane, toluene, 2-chloropropane, *o*-dichlorobenzene, and methylene chloride. It rises above 55% in chloroform, carbon tetrachloride, tri- and tetrachloroethylene, 1,1-dichloroethane, and 1,2-dichloropropane. Surprisingly, the reaction temperature affects negligibly the selectivity.³⁴

With the same reaction system ("claycop" and acetic anhydride), toluene, serving as its own solvent, is nitrated in 97% yield 44% ortho, 3% meta, and 53% para.³⁴ With carbon tetrachloride as the solvent, dilution has a profound influence on the regioselectivity. Going from 1 mL of toluene in 50 mL of solvent to the same amount in 2 L of solvent shifts the ortho, meta, para (o,m,p) product distribution from (42,2,56) to (23,1,76)! A similar effect is achieved by perfusion of 1 mL of toluene (0.6 mL·h⁻¹) in 50 mL of carbon tetrachloride, for a product distribution again favoring the para isomer, (20,1,79).³⁴ The explanation involves the high polarizability of carbon tetrachloride: at high dilution, it stabilizes the charged NO⁺ or NO₂⁺ electrophile by the (ion-polarizable distribution) electrostatic interaction, thus competing with the polarizable methyl group of toluene, whose own interaction of the same ilk with the electrophile tends to bring the substituent into the ortho position.³⁴ The process can be made catalytic. In mixed solutions of carbon tetrachloride and acetic anhydride, with a montmorillonite clay catalyst such as K10 or Eccagum BP, using a Dean–Stark trap to remove the water produced, nitric acid nitrates toluene in 81% yield with a (38.5,2.5,59) product distribution. The turnover is at least a factor 850.³⁵

Nitration of toluene and other alkylbenzenes by clay-supported metallic nitrates thus expresses a pronounced para preference. Can one go one step further with the

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Table II. Nitration of Alkylbenzenes by Benzoyl Nitrate in the Presence of a Morденite Zeolite

| substrate | GC yield, % | product distribution (o,m,p) |
|---------------------------|-------------|------------------------------|
| toluene | 99 | (32,1,67) |
| ethylbenzene | 100 | (25,2,73) |
| <i>n</i> -propylbenzene | 81 | (26,2,72) |
| <i>n</i> -hexylbenzene | 76 | (28,2,70) |
| isopropylbenzene | 86 | (14,2,84) |
| <i>tert</i> -butylbenzene | 76 | (5,3,92) |

help of shape-selective zeolites? The Swansea group³⁶ did: they used benzoyl nitrate as their reagent. Control experiments in the absence of any catalyst showed a sluggish reaction (4% yield only after 10 days), with a bizarre product distribution (o,m,p) of (55,35,10). Trials showed superiority of a large pore proton-aluminum-exchanged mordenite, in carbon tetrachloride solution. Another finding convergent with those of the Liège group³⁴ was the insignificant influence on regioselectivity of a decrease in the reaction temperature. A quantitative yield of mononitrotoluenes resulted within 4 min (!) of reaction at room temperature. The regioselectivities compared favorably to those achieved in Liège, especially for *tert*-butylbenzene (Table II). Even greater selectivities have been claimed recently by use of H-ZSM-11 zeolite treated with tributylamine.¹¹

Nitration of Halobenzenes. Halobenzenes traditionally³⁷ give a ca. (35,1,64) mixture of (o,m,p) nitroderivatives. The double challenge they offer is to cut down on the meta isomer and to boost the para/ortho ratio. A fresh look at the problem³⁸—and there is no room to present this analysis here in detail—concluded to the need to increase charge control. This could be achieved, it was felt, by lowering the dielectric constant of the medium. Accordingly, acetic anhydride was chosen as the desiccant. It has a dielectric constant of only 20, and it would evolve acetyl nitrate as the actual reagent. Low-dielectric solvents, hexane or methylene chloride, were chosen to look after the intimacy of nitronium (or nitrosonium) ion-halobenzene contact in the initially formed encounter complex.³³ The next step is the SET from the aromatic to the electrophile. The option of metallic nitrates would favor a radical cationic pathway, since metallic nitrates with covalent bidentate coordination of the nitrate group to the metal are powerful oxidants.³⁹ Thus, the system consisting of "claycop"²⁹ and acetic anhydride in a low-dielectric solvent was chosen. It led to high yields of nitrated products under very mild conditions, and with outstanding regioselectivities, as shown in Table III.

Chlorination

Reagents for Chlorination: The Active Species.

Molecular chlorine is the traditional reagent for chlorination of aromatic substrates.^{40,41} In the absence of added catalysts it reacts readily in an electrophilic

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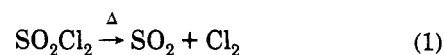
Table III. Product Distribution in the Nitration of Halobenzenes under Homogeneous or Heterogeneous Conditions

| substrate | product distribution (o,m,p) | |
|---------------|--|--|
| | heterogeneous ^a ("claycop" + A ₂ O) | homogeneous ^b (HNO ₃ -H ₂ SO ₄) ^b |
| fluorobenzene | (4,0,96) | (12,1,87) |
| chlorobenzene | (12,<0.4,88) | (30,1,69) |
| bromobenzene | (16,0,84) | (37,1,62) |
| iodobenzene | (30,0,70) | (38,2,60) |

^a Reference 38. ^b Reference 7.

manner only with activated aromatic compounds. Weakly activated or nonactivated substrates are generally reacted with chlorine in the presence of a Lewis acid such as AlCl₃ or FeCl₃. The Lewis acid complexes the chlorine to form a highly polarized species which in its extreme form may be represented as a chlorinium salt (e.g., Cl⁺ FeCl₄⁻). It is this highly polarized complex which is thought to be the active electrophilic reagent.^{40,41}

Sulfonyl chloride, by virtue of its being a liquid, is more easily handled than molecular chlorine. However, it is a milder reagent and reacts readily only with the most activated substrates such as phenols. Even then reactions are sluggish. At elevated temperatures it decomposes into sulfur dioxide and molecular chlorine (eq 1). Therefore, under forcing conditions reactions



characteristic of the free halogen may occur. There is evidence from kinetic studies, however, that under more moderate conditions the sulfonyl chloride itself acts as the electrophile.⁴²

A number of other types of chlorine-containing compounds have on occasion been used to effect ring chlorination of aromatics, including PhICl₂ in trifluoroacetic acid,⁴³ alkyl and acyl hypochlorites,⁴⁴ dichlorine monoxide (Cl₂O),⁴⁵ and *N*-chloroamines,⁴⁶ amides, and -sulfonamides.⁴⁷ Thus, the variety of possible chlorinating agents is wide.

A complicating feature is that many of the same reagents give other reactions as well. For example, sulfonyl chloride is used for chlorosulfonation of toluene,⁴⁰ while many of the reagents can lead to radical chlorination reactions, resulting in substitution in a side chain rather than on the ring, under conditions of higher temperature or irradiation with ultraviolet light.

Indeed, it was following the application of dichloramine-T as a radical chlorinating agent for organoboron compounds⁴⁸ that the Swansea group first became interested in the role of solids in organic reactions. Use of silica gel chromatography for purification of the

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product caused some new products to appear. Subsequent investigation revealed that the silica gel converted the dichloramine-T into an active electrophilic chlorinating agent.⁴⁹ This simple observation demonstrates that solids have the potential to alter reaction selectivity markedly. They may be able to switch a mechanism completely—from radical to polar, for example—or to influence the regioselectivity of the products formed by similar mechanisms.

Chlorination of Phenols and Anisoles. In its search for rationally designed supported reagents, the Swansea group elected *N*-chloro-*N,N*-dialkylamines as mild electrophiles for chlorination of phenols. More reactive chlorinating agents such as *tert*-butyl hypochlorite, sulfonyl chloride, or molecular chlorine were excluded, as they afford facile chlorination of activated substrates and consequently complex mixtures of isomers.⁵⁰ On the other hand, *N*-chloro-*N,N*-dialkylamines presented some scope for catalytic control, since the literature indicates that, in free solution, their rate of substitution is very slow and subject to a significant enhancement in the presence of mineral acid like HCl.⁵¹ Therefore, combinations of acidic silica gel with *N*-chloroamines were anticipated to produce good yields of selectively monochlorinated phenols. Indeed, encouraging results were obtained with *N*-chloromorpholine, -piperidine, and -*N,N*-diisopropylamine.⁵² When these reagents were used, the ortho/para ratio reached 5.0 with a monochlorination/polychlorination ratio of 2.3. Further enhancement was obtained with *N*-chloro-*N,N*-bis(2-chloroethyl)amine (NCBCE) as the chlorine source. Introduction of electron-withdrawing groups on the two carbons β to the nitrogen atom was thought to decrease the basicity of the amine, thus lowering its ability to complex phenol, and to increase the polarity of the N-Cl bond, so as to make the *N*-chloro-*N,N*-dialkylamine more electrophilic.⁵³ Experimental results matched this prediction: in conjunction with silica gel, NCBCE converts phenol into chlorophenols with an outstanding ortho selectivity (ortho/para = 12) and a favorable monochlorination/polychlorination ratio of 3.1. Although no attempts were made to optimize individual reactions, chlorinations of *o*-cresol and *o*- and *p*-chlorophenols displayed similar high selectivities.⁵²

Both the Liège and the Swansea groups have explored the chlorination of anisole in the presence of solid supports. By analogy with clay-supported metallic nitrates (see Nitration), the activity of metallic chlorides impregnated on the acidic K10 montmorillonite was investigated, using toluene and anisole as probe substrates.⁵⁴ As chloride anions lack the electrophilicity required for aromatic substitution, addition of a stoichiometric amount of oxidizer was called for. Nature resorts to hydrogen peroxide to activate chloride ions via the metallic center of porphyrin-based metalloen-

Table IV. Chlorination of Anisole under Various Conditions

| chlorinating agent (conditns) | yield, % | product distributn (o,p) | ref |
|--|-----------------|--------------------------|-----|
| Cl ₂ (room temp, CCl ₄) | nd ^a | (21,79) | b |
| <i>t</i> -BuOCl (room temp, CCl ₄) | nd ^a | (23,77) | b |
| SO ₂ Cl ₂ + ZF520 zeolite (reflux, neat) | 81 | (26,74) | 56 |
| <i>t</i> -BuOCl + SiO ₂ (25 °C, CCl ₄) | 100 | (30,70) | 57 |

^a Not determined. ^b Harvey, D. R.; Norman, R. O. C. *J. Chem. Soc.* 1961, 3604-3610.

zymes.⁵⁵ Transposing this observation to the laboratory, we elected *m*-chloroperbenzoic acid as the oxidizer. Among 13 metallic chlorides, anhydrous ferric chloride gave the best results.⁵⁴ Despite the ease of setup and workup associated with the use of a supported reagent, applications of this method are restricted by its lack of generality. More straightforward procedures had to be elaborated. The Liège group focused its attention on the use of sulfonyl chloride in the presence of the acidic zeolite ZF520,⁵⁶ while the Swansea group opted for *tert*-butyl hypochlorite in the presence of acidic silica gel.⁵⁷ Both methods are very easy to implement and give quantitative yields of monochlorinated derivatives for a wide range of substrates (further examples are given in the next section). Isomer distributions, however, reflect closely those produced by solution-phase electrophilic chlorinating systems, as illustrated in the case of anisole (Table IV). Somewhat improved para selectivity can be obtained by the use of *tert*-butyl hypochlorite in the presence of zeolites (see below).

Chlorination of Toluene and Other Normally Activated Hydrocarbons. Industrial syntheses of haloarenes are commonly performed with molecular chlorine in the presence of Lewis or mineral acids at 20–80 °C.⁴⁰ Catalysts such as aluminum(III), iron(III), tin(IV), or zinc(II) chlorides, to name just a few, have been used widely.⁵⁸ Besides the poor regioselectivities under these conditions, corrosion caused by these highly reactive species and by the hydrogen chloride side product is a major concern, not to mention disposal problems. Thus, a great deal of effort is being directed toward carrying out the halogenation of arenes in the gas and liquid phases using aluminosilicate catalysts, especially zeolites, in order to achieve better selectivities under milder conditions.⁵⁹ Irreversible damage caused to the zeolites by hydrogen halides is, however, a stumbling block, so that industrial applications are still rare.

The Swansea group has surveyed the catalytic activity of acidic silica gel upon aromatic chlorination by numerous inorganic and organic chlorine-containing compounds. Reactions were conducted with toluene as a probe-substrate at 25 °C in carbon tetrachloride. While most inorganic chlorides (AlCl₃, BCl₃, HgCl₂, LiCl, PCl₃, OPCl₃, SOCl₂, TiCl₄) and various organic derivatives (α -chloroacetamide and -acetone and *p*-toluenesulfonyl, oxalyl, and benzoyl chlorides) tested showed no sign of reaction after 2 days, use of *N*-chloro

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Table V. Product Distributions in the Ring Chlorination of Alkylbenzenes under Homogeneous or Heterogeneous Conditions in Carbon Tetrachloride at 25 °C

| substrate | product distribution (o,m,p) | |
|---------------------------|---|--|
| | heterogeneous ^a (<i>t</i> -BuOCl, SiO ₂ cat.) | homogeneous ^b (Cl ₂ , FeCl ₃ cat.) |
| ethylbenzene | (57,43) | (70,30) |
| isopropylbenzene | (44,56) | (59,41) |
| <i>tert</i> -butylbenzene | (15,85) | (11,89) |

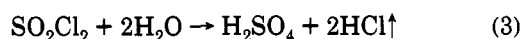
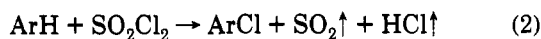
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Table VI. Chlorination of Alkylbenzenes by *tert*-Butyl Hypochlorite over HNaX Zeolite in Acetonitrile at 25-40 °C

| substrate | GC yield, % | product distribution (o,p) |
|---------------------------|-------------|----------------------------|
| toluene ^a | 95 | (8,92) |
| ethylbenzene | 100 | (10,90) |
| isopropylbenzene | 90 | (20,80) |
| <i>tert</i> -butylbenzene | 86 | (2,98) |

^a Reaction in diethyl ether.

derivatives, sulfuryl chloride, and hypochlorites led to the desired products. Comparison of the reaction rates further reduced the range of most reactive species in the presence of silica gel to sulfuryl chloride and *tert*-butyl hypochlorite.⁵³ Practical consideration contributed to the final choice, given that sulfuryl chloride is more sensitive to moisture than *tert*-butyl hypochlorite. Furthermore, the latter gives innocuous *tert*-butyl alcohol as byproduct, while HCl is released from SO₂Cl₂, either during the electrophilic substitution (eq 2) or by hydrolysis (e.g., with residual moisture from the solid) (eq 3).



The system *tert*-butyl hypochlorite/acidic silica gel proved to be a valuable reagent, able to chlorinate aromatic substrates of moderate reactivity with essentially quantitative yields of the nuclear monochlorinated derivatives.⁵⁷ As previously stressed (cf. Table IV), isomer distributions match those obtained under similar homogeneous conditions, as illustrated in Table V for selected alkylbenzenes.

Extending the research initiated with acidic silica gel, the Swansea group turned to acidic zeolites as shape-selective catalysts for aromatic chlorinations by *tert*-butyl hypochlorite. They elected the HNaX zeolite (i.e., a partially proton-exchanged NaX zeolite) for its pores large enough to accommodate aromatic nuclei (diameter ca. 0.74 nm) together with a high density of Brønsted acidic centers. Outstanding selectivities and quantitative yields were the fruits of this beneficial union. Indeed, reactions with halo- and alkylbenzenes give the highest para/ortho ratios ever achieved, as exemplified in Table VI.⁶⁰ Preparative chlorinations of toluene and chlorobenzene were also successful, while reuse of a spent catalyst after reactivation by calcination at 500 °C for 15 h showed no detrimental effect.⁶⁰

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Two experimental parameters deserve emphasis. First, the nature of the solvent used has a dramatic influence on the regioselectivity. Switching from the nonpolar *n*-pentane (polarity = 0.1 D) to the strongly polar acetonitrile (polarity = 3.12 D) results in a change of para/ortho ratio from 63/37 to 78/22 for toluene chlorination. Even greater para selectivity (para/ortho up to 92/8) stems from introduction of diethyl ether in the reaction mixture. Unfortunately, the use of ether as a solvent or cosolvent is not recommended with less reactive aromatic substrates than toluene, because free-radical reaction of *tert*-butyl hypochlorite with the ether then becomes competitive. A second noteworthy point, less crucial, is the influence of the zeolite crystallinity on the product distribution. Here, the explanation is straightforward. Use of larger crystals maximizes the internal surface available and, consequently, helps control the regioselectivity by favoring intracrystalline reactions. Thus, synthesis of a catalyst characterized by a mean particle diameter of 7 μm led to a para/ortho ratio of 94/6, while smaller crystals of average size 1 μm give a para/ortho ratio of 92/8 under otherwise comparable conditions.⁶¹

Due to their large diversity of composition and structure, zeolites can display outstanding catalytic prowess even in the absence of shape selectivity. Indeed, a simple change in the silicon-to-aluminum ratio and/or the nature of the exchangeable cations may lead to a dramatic change in the reaction pathway. This was experienced by the Liège group in a study of aromatic chlorination by sulfuryl chloride in the presence of Y type zeolites.⁵⁶ Taking toluene as an example, the action of SO₂Cl₂ can result in (i) an electrophilic substitution of the aromatic ring or (ii) a side-chain halogenation of the methyl group. The first pathway is *ionic* and gives rise to chlorotoluenes. The presence of an acidic catalyst is required, because toluene is not a highly activated substrate. The alternate route affords benzyl chloride. It follows a *radical* pathway and demands the presence of a radical chain initiator. Channeling the reaction into one or the other of these two competing pathways can be accomplished by carefully adjusting the properties of a zeolite catalyst. Recourse to the industrial ZF520 variety (a faujasite type zeolite with a Si/Al ratio of 20 containing proton counterions) provides a strongly acidic catalyst: its measured surface acidity is intermediate between -3 and -5.6 in the Hammett *H*₀ scale,^{62,63} equivalent to 48-71 wt % sulfuric acid.⁶⁴ Addition of this solid to a mixture of toluene and sulfuryl chloride and refluxing in the dark during 30 min gives an 80% yield of chlorotoluenes, accompanied by only 0.05% of benzyl chloride, i.e., a predominance of nuclear over side-chain chlorination of 1600/1. The (o,p) distribution of (63,37), close to the statistical (67,33) value, denotes the absence of shape selectivity and strongly indicates that the reaction occurs on the outer surface of the catalyst.

Taking again the chlorination of toluene as an example, it is possible completely to reverse the chemoselectivity, simply by substituting the NaX

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Table VII. Side-Chain Chlorination of Alkylbenzenes by Sulfuryl Chloride in the Joint Presence of Zeolite NaX as Catalyst and a Visible Light Source

| substrate | GC yield, % | products |
|---------------------------|-------------|--|
| <i>o</i> -xylene | 68 | α -chloro- <i>o</i> -xylene |
| <i>m</i> -xylene | 70 | α -chloro- <i>m</i> -xylene |
| <i>p</i> -xylene | 77 | α -chloro- <i>p</i> -xylene |
| ethylbenzene | 83 | α -chloroethylbenzene |
| | 15 | β -chloroethylbenzene |
| <i>tert</i> -butylbenzene | 70 | β -chloro- <i>tert</i> -butylbenzene |

zeolite for the ZF520 variety. The faujasite type network is preserved, but we now deal with a pure sodium form of a high aluminum material (Si/Al = 1.25). The acidic properties have therefore almost vanished ($2.8 < H_0 < 6.8$, equivalent to $\approx 10^{-4}$ – 8×10^{-8} wt % H_2SO_4 ⁶⁴), while the proportion of $O_3Si-O-AlO_3$ groups is close to the maximum. These groups are more likely to undergo homolytic cleavage into $O_3SiO\cdot + O_3Al\cdot$, thus generating silyloxy radicals.⁶⁵ These would serve as the catalytic centers to initiate a radical chain reaction. Indeed, refluxing a suspension of NaX molecular sieve in toluene and sulfuryl chloride, only complemented with visible light irradiation, affords specifically benzyl chloride in a ca. 80% yield.⁶⁶ The experimental procedure is easily modified to chlorinate further toluene into benzal chloride ($PhCHCl_2$) or benzotrichloride ($PhCCl_3$) with good selectivities. Other examples of side-chain chlorinations are provided in Table VII. The procedure has been successfully applied to the large-scale preparation of α -chloro-*p*-xylene.⁶⁶

X-ray diffraction studies clearly indicate that the zeolite lattice collapses when exposed to the drastic reaction conditions (HCl and SO_2 are evolved from a refluxing mixture at ≈ 110 °C).⁶⁶ Therefore, shape selectivity is out of the question. Yet, it is worth mentioning that the degradation products of the original NaX zeolite (NaCl, $NaAl(SO_4)_2 \cdot 6H_2O$, and uncharacterized amorphous materials) are also efficient catalysts for the side-chain chlorination. Recycling experiments have demonstrated that they can be recovered and

reused at least 10 times with no significant loss of activity.^{66,66}

Chlorination of Halobenzenes. The industrial preparation of *p*-dichlorobenzene and other polyhalogeno derivatives generally involves multiple chlorination of benzene or of other suitable starting materials. The number of chlorine atoms introduced is hard to control, so that mixtures of products are frequently obtained.⁶⁷ In contrast, the selective formation of *p*-dihalobenzenes can be easily accomplished in the laboratory. So far, the prize for highest para selectivity in the chlorination of chloro- and bromobenzenes goes to the Swansea group. Recourse to the combination of *tert*-butyl hypochlorite and HNaX zeolite proved to be even more successful with halo- than with alkylbenzenes, affording ortho and para products in the proportions of 3/97 (para/ortho = 32) for both chloro- and bromobenzenes as substrates.⁶⁰

Conclusions. We have shown that extremely significant improvements in the regioselectivity of aromatic substitution are feasible through the use of rationally selected solid supports and catalysts. Among these, zeolites are an important class. Their import from industrial chemistry and their domestication within academic chemistry offer considerable promise. Zeolites are extremely useful for their shape selectivity, but they can be useful also when their involvement is limited to their outer surface. Other catalysts, such as clays, can be used to advantage. The effectiveness of all these heterogeneous catalysts is a sensitive function of the nature of the solvent. This poorly understood parameter is crucial to continued progress in this area. It is one of the obvious and most promising avenues for future research. While the studies that we have summarized here had preparative rather than mechanistic purpose, they have helped us to bring into focus the important factors in the reaction mechanism. In this respect, the proposal championed by Perrin of a radical cationic access to the arenium Wheland intermediate in nitration reactions is nicely consistent with some of our results.

We thank our co-workers whose names are listed in the references for their enthusiasm and trust. Fonds de la Recherche Fondamentale Collective, Brussels, gave support to the Liège group at a crucial time, and the writing of this Account was vastly aided by a Ciba-Geigy Fellowship Trust "ACE" Award to one of us (K.S.).

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