0.34 g (4.0 mmol) of NaHCO₃ and 0.28 g (1.5 mmol) of tetra-ethylammonium chloride in 30 mL of dry dichloromethane. The reaction was immediately quenched by the addition of 30 mL of water. The layers were separated, and the organic layer was washed three times with 20 mL of water. The organic layer was dried over MgSO₄ and filtered and the solvent removed by rotary evaporation. The residue was dissolved in CDCl₃ and analyzed by NMR.

Vastly Improved Para Preference in the Nitration of Halobenzenes

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The halobenzenes are mononitrated with cupric nitrate supported on the K10 montmorillonite in the presence of acetic anhydride, in hexane, or in methylene chloride, at room temperature or below. Good isolated yields (50-75%) are accompanied by much improved para selectivities, up to a para-to-ortho ratio of 35 (a selectivity factor of 70) for fluorobenzene. The observed selectivity factors are determined uniquely by the polarizability of the halogen substituent.

Most aromatic nitrations, as classically performed with mixtures of nitric and sulfuric acids, give predominantly ortho and para products. Quite often their distribution is close to the statistical 2:1 ratio.[1] Yet it is desirable to improve the regioselectivity, pushing it toward a higher proportion of the para product. Our start in this direction was nitration of phenols by "clayfen",[2] i.e., clay-supported ferric nitrate. It gave significantly greater para/ortho ratios than other procedures.[3] We address now a similar goal for the converse case of aromatic systems deactivated by electron-withdrawing substituents, the halobenzenes.

This work is part of a more general program for renovating the important reactions of organic chemistry, using silicates as supports and catalysts.[4] For this purpose we

Table I. Product Distribution in the Nitration of Halobenzenes[1a]

	product		
substrate	ortho	meta	para
fluorobenzene	12		87
chlorobenzene	30	0.9	69
bromobenzene	37	1.2	62
iodobenzene	38	1.8	60

bring to bear principles and rules of physical chemistry. The present advance is based on the simple notions of charge control and of the electrostatic interaction of a charge with a polarizable distribution. From such conceptual simplicity, one can learn how to master the reaction outcome. Thus, it becomes easy to steer it to the formation of the most desirable product, under the gentlest of conditions.

1. Background

Halobenzenes are deactivated for electrophilic aromatic substitution, they react slower than benzene. Nevertheless, the halogen substituents are ortho-para directing.[1] The explanation given to this paradox (or Holleman anomaly[1a]) invokes the Hammond postulate to assume that the transition state resembles the Wheland (arenium ion) intermediate.[5] The arenium ions conducive to ortho or para products are stabilized by delocalization of the lone pairs from the halogen substituents.[6] The observed para preference, according to this interpretation, stems from the greater contribution of para-quinonoid as compared to ortho-quinonoid limiting forms, in the resonance description.[5] The proportion of para product is the highest for fluorobenzene and the smallest for iodobenzene.[7] This is interpreted by greater relative deactivation due to the inductive effect of the substituent at the ortho than at the more remote para position, in consonance with fluorine

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having the strongest $-I$ effect of the four halogens.[5,6]

In other terms, this traditional semiquantitative explanation focusses alternately on the inductive and resonance effects of the substituents. The decreased reactivity is blamed on the former being predominant. The ortho–para directing influence is seen as the reflection of the resonance term. The para preference is also seen as the consequence of resonance, but *the magnitude* of the para preference is attributed to the inductive effect.[8]

2. Statement of the Problem

The goal is to raise the proportion of the para product. Its present economic importance warrants it.[9] Nitrohalobenzenes have much industrial use. Both functionalities can undergo further transformations. For instance, *p*-chloronitrobenzene is converted into the nitrophenol by aqueous sodium hydroxide.[10]

Yet, the para preference is modest under classical nitration procedures (Table I) and it has remained modest with more recent procedures. Could one improve it markedly and go beyond the factors 2–5 that have been obtained so far?[7]

A first line of attack is totally unpromising: steric effects are (close to) inoperative in the nitration of the halobenzenes[1,5] as consideration of Table I makes it apparent; iodobenzene, in which the bulky halogen might be expected to deter from ortho substitution, shows the greatest percentage of ortho nitration product.

A second, related ploy would probably be much more effective: use encapsulation of the aromatic substrate in an auxiliary inclusion compound in order to block ortho attack and favor thus formation of the para product. Breslow has used cyclodextrins very successfully in this way.[11] Likewise, Masci[12,13] has obtained significantly improved para selectivities by complexing the nitronium ion with the 21-C-7 crown ether, in an apparent successful application of the reactivity–selectivity principle.[14] The drawback of this concept (to put a glove on either of the reaction partners) is the expense of the glove, which probably makes it prohibitive for large-scale industrial applications.

A third approach does not appear to be applicable here. Since the transition state, in abeyance of the Hammond postulate, is a late arenium ion-like transition state for these sluggish reactions, one cannot devise para selectivity on the basis of the frontier molecular orbital for the aromatic reactant molecules. Consideration conversely of the localization energies in the arenium ions is not very helpful here either: the intellectual contortions of Ingold to explain away the Holleman anomaly in valence-bond terms[1a] are only matched by the difficulty of MO theory to account quantitatively for the ortho–para preference in the nitration of chlorobenzene.[15]

Or, to put it in another way, substituent effects (inductive, or field; and resonance) are characteristic of the

isolated molecule and cannot be modified easily. Hence, they provide no good handle on the localization energies.

Fourth and last, a solution of last resort, rarely tried in preparative chemistry, is to change the mix between orbital control and charge control.[16] In the case at hand, the likely nitronium ion intermediate NO_2^+ has a most attractive peculiarity. Its electron affinity (9.8 eV[17]) makes it a soft Lewis acid. The halobenzenes, with first ionization potentials below 9.2 eV,[18] are Lewis bases of intermediate hardness, from 4.84 eV for bromobenzene to 5.04 eV for fluorobenzene.[19] Hence, the interaction of NO_2^+ with halobenzenes is best described as a combination of covalency (orbital mixing) and electrostatics. Accordingly, our idea is to increase charge control, i.e. the electrostatic component, simply by lowering the dielectric constant.

3. Outline of a Solution

A remarkable feature of halobenzenes is the strong electronic polarization by the substituent. It can translate into considerable kinetic differentiation among ring carbons. For instance, the relative rates of protium–deuterium exchange in KNH_2/NH_3 are[20]

C_6H_5D	p-C_6H_4DF	m-C_6H_4DF	o-C_6H_4DF
1	200	4000	4 000 000

It is thus tempting to take advantage of the strong polarization by the substituent to boost the para preference.

What is then required is to increase the relative amount of the electrostatic contribution to the total interaction energy. In the Klopman formalism,[16] this means increasing the weight of the first, electrostatic term in eq 8 of his paper. Lowering the effective dielectric constant is probably the simplest means to such a goal.

Now we have to be more specific: what class of nitrating agent should we use? We have elected metallic nitrates, because of our earlier success in nitrating phenols with improved para regioselectivity.[3] We had used ferric nitrate for this purpose, but other authors have had good success in nitration of aromatics using a variety of metallic nitrates. Titanium(IV) nitrate is a recent example.[21]

A quick flashback to our earlier work is in order here. The main rationale for using clay-supported ferric nitrate ("clayfen"[2]) on phenols[3] had been the favoring of a radical cation pathway, combining a smectite clay support well-known to promote radical cation formation[22] and a cova-

(8) How confusing, even if ample support can be mustered for each of these propositions. Students should not be blamed for having trouble in learning organic chemistry, nor at beating us at our games of explaining away any result with the deft application of inductive, resonance, and steric effects in the appropriate dose!

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lent metallic nitrate with high oxidizing prowess: Addison's group has shown that metallic nitrates with covalent bidentate coordination of the nitrato groups to the metal are powerful oxidants.[23]

This feature requires that the metallic nitrate be anhydrous, since hydration favors ionic to the detriment of covalent structures. The "clayfen" reagent was a compromise in this respect, since the montmorillonite support gave needed stability to the hyperactive anhydrous ferric nitrate[2] but at the same time unavoidably introduced humidity in the system. An obvious means for boosting the reactivity of the nitrating agent, therefore, is to use more rigorous dehydrating conditions.

As early as 1925, Menke devised reaction conditions for nitrations by metallic nitrates close to our needs and conducive to high yields of nitro products:[24] use of cupric nitrate,[25] or of other metallic nitrates,[23] dissolved in acetic acid/acetic anhydride, so that water introduced with the inorganic salt is absorbed by the anhydride.

We note here that acetic anhydride, besides sponging up excess water, will also lower greatly the dielectric constant: water has a dielectric constant of 78, while that of acetic anhydride is only 20. Because we had also tested successfully this reagent in the nitration of aromatic hydrocarbons,[27] we have opted for a variant of "claycop"[2] (clay-supported cupric nitrate[27]) in the presence of a copious amount of acetic anhydride. In order to further lower the dielectic constant of the medium, it is advisable to use a low-dielectric solvent[28] such as hexane or methylene chloride. With such a choice for the solvent, our new reagent is fully defined. This reagent is made from readily available components, it is much easier to handle than titanium(IV) nitrate[21] and it leads to high yields of nitrated products under very mild conditions, and with outstanding regioselectivities.

4. Experimental Section

General Information. All starting materials and their nitro derivatives were commercially available and were used without further purification. Melting points were taken on a Mel-Temp apparatus. Infrared spectra were recorded on a Perkin-Elmer 1320 infrared spectrometer. NMR spectra were obtained on a Bruker AM-300 spectrometer in $CDCl_3$ solution. The gas chromatograph, Intersmat IGC 121FL, was equipped with a flame ionization detector and a capillary column (length 26 m, inside diameter 0.32 mm, liquid phase OV1701). Column chromatography was performed by using Macherey-Nagel silica gel 60 (70–230 mesh).

Preparation of Clay-Supported Cupric Nitrate.[27] In a 1-L pear-shaped evaporating flask, copper(II) nitrate trihydrate (26 g) is added to acetone (400 mL), and the mixture is vigorously stirred for ca. 5 min. K10 clay (Süd-Chemie) (30 g) is then added,

Table II. Yields and Reaction Conditions for Nitration of Halobenzenes by Clay-Supported Cupric Nitrate

substrate	solvent	reactn times	isolated yields in nitro products (%)
fluorobenzene	*n*-hexane	48 h	53
chlorobenzene	*n*-hexane	48 h	73
bromobenzene	*n*-hexane	30 h	74
iodobenzene	dichloromethane	7 days	38

Table III. Para/Ortho Ratios in the Nitration of Halobenzenes

methods	C_6H_5F	C_6H_5Cl	C_6H_5Br	C_6H_5I
"claycop" (this work)	25	7.5	5	2.3
HNO_3/H_2SO_4[29]	6.6	1.8	1.3	1.2
$AgNO_3/BF_3$[30]	2.7	1.3	3.0	4.7
NO_2BF_4/sulfolane[31]	10.8	3.5	2.8	1.8
$A_2ONO_2/MeNO_2$[29]		2.3	1.7	1.6
HNO_3/Ac_2O[24]		9.0	3.0	
HNO_3/Nafion-H[32]		1.6	1.2	

and stirring is continued for another 5 min. The evaporating flask is connected to a rotary evaporator, and the solvent is eliminated under reduced pressure, on a water bath at 50 °C. After ca. 15 min, a dry solid crust adheres to the walls of the flask. It is flaked off with a spatula, and the rotary drying under vacuum is resumed for 30 min at the same temperature. This yields the clay-supported copper nitrate reagent as a blue free-flowing powder, which shows no loss of reactivity for several weeks.

General Procedure for Nitration of Halobenzenes. To a solution of the halobenzene derivative (10 mmol) in *n*-hexane (50 mL) (or dichloromethane in the case of iodobenzene) are added acetic anhydride[26] (100 mmol) and clay-supported copper nitrate (5 g). The mixture is stirred vigorously at room temperature and, after reaction (for reaction times, see Table II), filtered under reduced pressure. The reagent is washed with portions of solvent. The nitro compounds are separated by column chromatography on silica gel, using a mixture of cyclohexane and ethyl acetate (usually 9/1 v/v) as eluent; they are identified by comparison (TLC, capillary GC, mp, or IR) with authentic samples.

5. Results and Discussion

The results are listed in Tables II and III. The reader should make a mental note of an important point: with potential industrial application in mind, we have not striven to optimize the procedure as to yields or selectivities. Undoubtedly, these can be and will be further improved. We content ourselves with showing here that a reagent consisting of simple materials gives good results under extremely mild conditions (at room temperature). Indeed, the isolated yields are fairly good, and, even more important, the para preference is greatly increased. Let us note in passing that metallic nitrates[33] and the Menke conditions[34] are known to give *high* (ortho/para) ratios. Our results run contrary to this pattern, which points to the extreme importance of the clay: not only does it serve as a support, leading to greatly increased encounter rates through two-dimensional diffusion[35] it also modifies reaction selectivity.

The question that springs to mind upon examination of the regioselectivities in Table III is the origin of the smooth decrease in the ratio of para to ortho product, in going from

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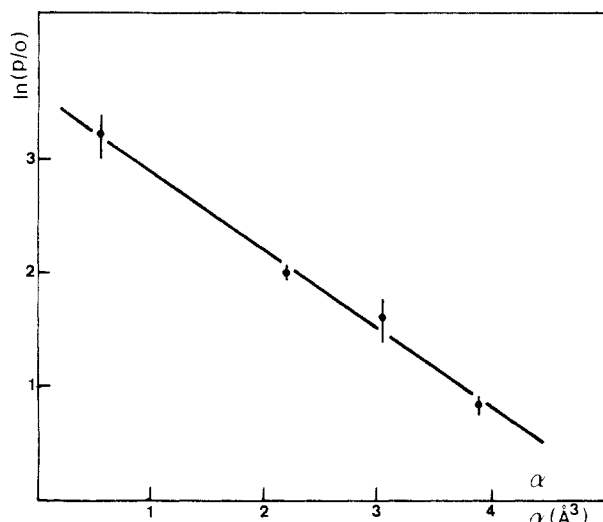
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Figure 1. Plot of ln (p/o) as a function of the polarizability α[37] of the substituent (correlation coefficient = 0.996).

the fluoro to the iodo substituent. This variation is amenable to a simple explanation, on the basis of electrostatics. For this purpose, let us assume an invariant distance r between the attacking positively charged electrophile and the attacked aromatic ring. The interaction between the positively charged nitronium ion and a polarizable electronic distribution is of the form[36]

$$E = -\frac{1}{2} \frac{1}{4\pi\epsilon_0} \frac{\alpha q^2}{\epsilon_R r^4}$$

Because of the dependence on the inverse fourth power of the distance, this attractive interaction will increase the relative amount of the ortho isomer, the more so the bigger the polarizability α of the substituent. This argument leads to the prediction of the linearity of $\Delta G° = -kT$ ln (o/p) with E, or, with the above assumption, with the polarizability α of the halogen substituents.[37] This model is found to account extremely well for the observed regioselectivities (Figure 1).

Furthermore, this extremely clean correlation (Figure 1) is not unanticipated. As Ingold pointed out in 1953, "the electron displacements by (mesomeric) mechanism are essentially electromeric displacements, +E, stimulated by the electrophilic reagent, and ... they become important only at those moments at which the reagent is already at an ortho or a para position, and is there committed to ortho or para attack. So we may expect this major difference of selectivity between polarization and polarizability effects: the latter operate only *where* the reagent is and only while it is there. In electrophilic aromatic substitution, the conjugate displacements to reaction centres at ortho or para positions are essentially polarizability effects".[1a]

Now we can also offer an easily understood explanation of the product distribution: the greater stability of the para arenium ion dictates the para preference. As a countervailing tendency, the polarizable halogen pulls the entering group next to it into the ortho position.

We note also that the regression shown in Figure 1 vindicates a posteriori our working hypothesis, viz. that the charge-control and the orbital-control terms in the Klopman expression[16] are comparable in magnitude, so

that a reduction in the dielectric constant of the medium is expected to make electrostatic interactions predominant. Given the assumptions and the approximations implicit in the very simple model behind Figure 1, its quantitative analysis must be taken with some caution. We cannot help noting however that the plot extrapolates to a para preference of ca. 36 ($e^{3.6}$) at room temperature for an ideal substituent with zero polarizability, a not unreasonable result.

As for the slope of Figure 1, it indicates a center-to-center distance between the electrophile and the halogen substituent of 2.5 ± 0.5 Å when the "effective" dielectric constant spans the whole range of 5 to 20, appropriate to our experimental conditions. While this distance should be taken as an order-of-magnitude only, it nevertheless fits beautifully the notion of van der Waals contact between the approaching electrophile and the aromatic system, which again is a reasonable conclusion.

Rational design of reaction conditions, besides being intellectually satisfying, has also programmatic value. It can point to further improvements. In the case at hand, we can state two such directions for future work. The first is to cajole the recalcitrant iodobenzene into a greater para preference, even though the charge–polarizability interaction plays in favor of its ortho competitor. A possible answer is to increase the distance of approach r, in order to decrease the contribution from this component. This could be done in the Masci way[12,13] by wrapping a suitable crown ether around the nitronium ion. A second and even more obvious move is to further increase the para preference by lowering the temperature. It works handsomely, as we have tested already on the fluorobenzene case: lowering the temperature from room temperature (20 °C) to 0 °C increases the para preference from 25 (Table III) to 35, with an overall isolated yield of 59% for a reaction time of 72 h.

Last but not least, we emphasize that such results are achieved with low–cost reagents and materials. The regioselectivities obtained with our novel procedure enable a decrease in the unit cost of the target para product, with comparison to the silver nitrate–boron trifluoride system (Table III) by a factor of ca. 2.

Conclusion

The necessary ingredients for boosting the proportion of para nitro product from the halobenzenes are the lowering of the (i) temperature; (ii) dielectric constant of the medium; and (iii) dimensionality of the reaction space. There is a limit to the increase of the para preference. It is set only by the polarizability of the halogen which favors the alternate ortho entry.

Our new procedure has conceptual simplicity. It commends itself also for its operational simplicity: workup consists solely in a filtration, followed by separation of the two regioisomers. It gives rise only to products of *mono*-nitration, another advantage. Given the economic importance of nitrated aromatics, the methodology devised here may go beyond a mere academic exercise in problem-solving; it could be useful as well.

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