

THE SELECTIVITY OF ELECTROPHILIC AROMATIC NITRATION
AND THE EFFECT OF THE ORGANIC SOLVENTS

Bernardo Masci

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

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Abstract - The nitrating agent prepared by mixing Bu_4NNO_3 and $(\text{CF}_3\text{CO})_2\text{O}$ has been used to nitrate in homogeneous conditions eight aromatic substrates, ranging in reactivity from benzene to mesitylene, in several organic solvents. From competitive kinetic experiments and glc analysis, partial rate factors were obtained. The nature of the solvent significantly affects selectivity in the whole activation range. Selectivity was quantitatively measured by the selectivity factor for toluene, and, more properly, by the slopes in the correlations between log values of partial rate factors in a given solvent and the corresponding values in a reference solvent. Good correlations were obtained also including ortho positions and polysubstituted substrates, and the following order of relative selectivity could be established: $\text{MeNO}_2 < \text{MeCN} \leq \text{sulfolane} < \text{CH}_2\text{ClCH}_2\text{Cl} < \text{CH}_2\text{Cl}_2 \leq \text{EtOAc} \leq i\text{-PrBr} = n\text{-BuCl} = n\text{-BuBr} \leq \text{CHCl}_3$. Correlation between partial rate factors has been extended to compare the selectivity of different nitrating agents in the same solvent, and the method can be used to ascertain whether the same electrophilic species actually operates in the two systems.

In our previous investigations on electrophilic aromatic nitration,^{1,2} crown ethers were shown to deeply influence, through both electronic and steric effects, the substrate and the positional selectivity of the complexed NO_2^+ ion. In order to fully rationalize the effect of the added ligands, the intriguing problems that selectivity of electrophilic aromatic nitration³ presents even in their absence must be faced. A well known peculiarity of this reaction is that substrate selectivity vanishes for activated compounds, whilst positional selectivity survives, and the rate determining formation of an intermediate preceding the σ adduct formation is commonly believed to occur. The intermediate has been given the characters of a π complex,⁴ of an encounter pair,⁵ or of a radical-radical cation pair,^{6,7} and the fact that the selectivity behaviour is little affected on changing the conditions can be attributed to the operation of the same electrophilic species, namely the NO_2^+ ion.³ Actually a number of nitrating agents in organic media

have been studied, besides the popular $\text{HNO}_3\text{-Ac}_2\text{O}$ mixture, which are more selective towards activated substrates than $\text{HNO}_3\text{-H}_2\text{SO}_4$ and the like, and for them it is not clear whether NO_2^+ is the electrophilic species or not.⁸⁻¹³ The picture is complicated by the fact that various organic solvents are used and that the role of the solvent in the selectivity behaviour has not been systematically investigated.¹⁴

In the present paper we describe an empirical approach to the selectivity in electrophilic aromatic nitration of activated substrates, which starts from the investigation of the solvent effect.

RESULTS AND DISCUSSION

A nitrating agent has been used which allows electrophilic aromatic nitration to be carried out in homogeneous solution in a variety of organic solvents. This is the mixture of Bu_4NNO_3 and trifluoroacetic anhydride (TFAA) we previously reported,² and could be employed in three dipolar aprotic solvents, in ethyl acetate, and in several halogenated solvents. The substrates investigated ranged in reactivity from benzene to mesitylene: equimolar amounts of a pair of substrates were reacted in competitive kinetic experiments with the nitrating agent in each of the solvents, and the mononitrated products which cleanly formed were quantitatively analyzed by glc. The aromatic substrates were in excess with respect to the nitrating agent, so that the ratio of the nitrated products yielded the relative rates. Through the suitable pairing of the substrates, the rates were referred to benzene, and, from the isomer distribution, the partial rate factors could be determined. The results are reported in Table 1. Some of the tested solvents (mostly solvents 4, 6, 7, 8, and 9) are quite unusual as reaction media for aromatic nitration: in particular the structural modifications in monohaloalkanes were carried out with the aim at finding special selectivity effects, but all the tested members of the family behaved similarly (even 1-chlorooctane, not reported in Table 1). A number of interesting selectivity features are apparent on inspection of Table 1: i) whatever the solvent, the reaction shows substrate selectivity in the whole examined activation range; ii) both the substrate and the positional selectivity are affected by the change in the medium, and marked effects are present, for instance on the para/meta ratios in monoalkylbenzenes; iii) the selectivity in halogenated solvents and in EtOAc is distinctly higher than in dipolar aprotic solvents; iv) in all cases the reaction with $\text{Bu}_4\text{NNO}_3\text{-TFAA}$ conforms to the general selectivity pattern of electrophilic aromatic nitrations, and the correlation with the σ^+ values fails for such highly activated

positions as $p\text{-OCH}_3$.

Due to the difficulties connected with point iv, a standard criterion is lacking for a quantitative measure of selectivity: actually the breakdown of the correlation with the σ^+ values has somewhat discouraged the use of linear free energy relationships in general, in electrophilic aromatic nitrations, and often the comparison between the selectivity of the various agents is carried out by direct tabulation of relative rates and isomer distribution. We shall use two linear free energy relationships to quantitatively study the selectivity in the various solvents: the classical Brown's selectivity relationship for toluene¹⁵ is shown in Fig. 1. It is seen that the changes in substrate and positional selectivities are correlated on changing the solvent. The experimental points are fairly close to the expected straight line and the selectivity factor spans a wide range ($\log (f_p/f_m)$ changes from 1.24 to 1.89).

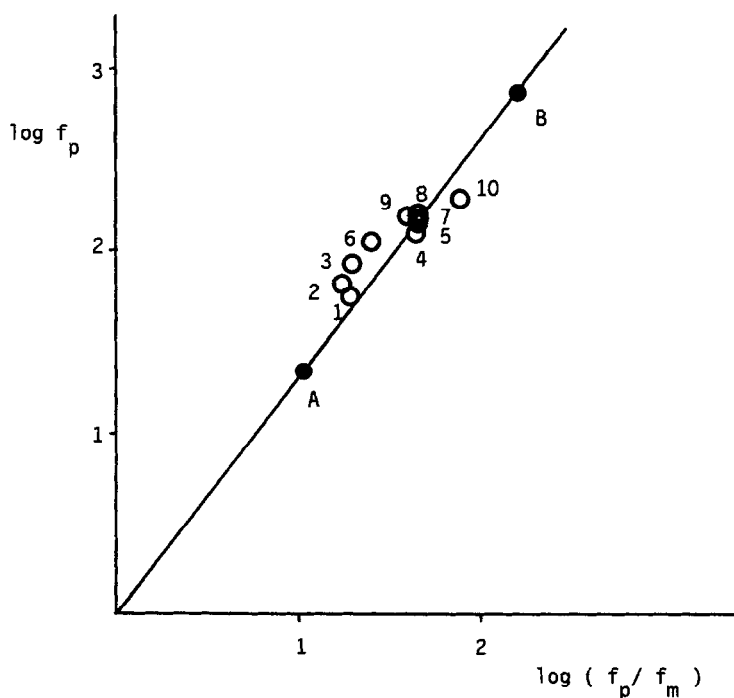


Fig. 1. The fit to the Brown's selectivity relationship on changing the solvent in toluene nitration. The numbers refer to the solvents in Table 1. Representative points are given for poorly and highly selective electrophilic aromatic substitutions: A, mercuration with $\text{Hg}(\text{OAc})_2$ in AcOH ¹⁶; B, chlorination with Cl_2 in AcOH ¹⁷.

Table 1. Rates Relative to Benzene and Isomer Distribution for Aromatic Nitration with Bu_4NNO_3 - TFAA in Various Organic Solvents at 25 °C.

	1	2	3	4	5
	MeNO_2	MeCN	Sulfolane	$\text{CH}_2\text{ClCH}_2\text{Cl}$	CH_2Cl_2
Toluene					
k_{rel}	25.9	33.9	42.4	49.7	57.6
% <u>o</u> -nitro	60.6	63.6	63.1	56.4	57.4
% <u>m</u> -nitro	3.8	3.7	3.4	1.8	1.8
% <u>p</u> -nitro	35.7	32.7	33.6	41.7	40.9
Ethylbenzene					
k_{rel}	21.7	27.8	35.7	45.9	52.8
% <u>o</u> -nitro	45.6	49.4	48.1	45.0	47.2
% <u>m</u> -nitro	5.4	5.9	4.8	2.4	2.1
% <u>p</u> -nitro	49.0	44.7	47.0	52.6	50.8
<i>i</i>-Propylbenzene					
k_{rel}	16.7	20.5	27.6	38.5	44.1
% <u>o</u> -nitro	24.0	27.4	25.4	24.6	24.9
% <u>m</u> -nitro	7.6	8.7	7.2	3.1	2.6
% <u>p</u> -nitro	68.4	63.9	67.4	72.3	72.5
<i>t</i>-Butylbenzene					
k_{rel}	14.7	17.3	24.2	32.9	41.0
% <u>o</u> -nitro	11.5	11.2	11.4	10.8	12.2
% <u>m</u> -nitro	11.7	14.5	11.8	5.3	4.7
% <u>p</u> -nitro	76.8	74.2	76.7	83.9	83.0
<i>m</i>-Xylene					
k_{rel}	193	321	475	667	963
% 2-nitro	16.0	16.9	15.8	15.9	16.0
% 4-nitro	84.0	83.1	84.2	84.1	84.0
Anisole					
k_{rel}	259	788	702	1460	2460
% <u>o</u> -nitro	65.0	72.6	66.3	77.6	80.5
% <u>p</u> -nitro	35.0	27.4	33.7	22.4	19.5
Mesitylene					
k_{rel}	620	1510	2180	2990	5200

Table 1: continued

	6	7	8	9	10
	EtOAc	<u>i</u> -PrBr	<u>n</u> -BuCl	<u>n</u> -BuBr	CHCl ₃
Toluene					
k_{rel}	49.5	60.9	63.4	60.1	71.0
% <u>o</u> -nitro	59.0	56.5	55.3	54.5	54.0
% <u>m</u> -nitro	3.0	1.8	1.8	2.2	1.2
% <u>p</u> -nitro	38.0	41.7	42.9	43.3	44.9
Ethylbenzene					
k_{rel}	40.2	60.1	59.5	57.0	69.3
% <u>o</u> -nitro	44.8	44.0	42.6	42.2	41.5
% <u>m</u> -nitro	4.1	2.4	2.4	2.2	1.7
% <u>p</u> -nitro	51.1	53.6	55.0	55.6	56.8
<u>i</u> -Propylbenzene					
k_{rel}	31.8	49.7	52.0	51.4	60.7
% <u>o</u> -nitro	22.8	23.5	22.0	21.9	22.8
% <u>m</u> -nitro	5.8	3.0	3.0	2.8	2.1
% <u>p</u> -nitro	71.4	73.5	75.0	75.3	75.2
<u>t</u> -Butylbenzene					
k_{rel}	27.3	45.4	45.1	46.8	52.6
% <u>o</u> -nitro	8.6	11.3	8.5	8.5	9.3
% <u>m</u> -nitro	10.4	5.3	5.2	5.1	3.6
% <u>p</u> -nitro	81.0	83.4	86.4	86.5	87.1
<u>m</u> -Xylene					
k_{rel}	888	1270	1070	1190	1530
% 2-nitro	13.9	15.0	13.4	13.8	13.2
% 4-nitro	86.1	85.0	86.6	86.2	86.8
Anisole					
k_{rel}	5320	4910	5440	5200	5910
% <u>o</u> -nitro	77.8	81.0	81.7	81.9	76.8
% <u>p</u> -nitro	22.2	19.0	18.3	18.1	23.2
Mesitylene					
k_{rel}	6620	8940	8810	9260	10200

In order to quantitatively measure the selectivity in all the activation range as a function of the solvent, log values of partial rate factors in the various media have been correlated: such a correlation has been extended to ortho positions and also to polysubstituted substrates. *n*-BuCl has been chosen as the standard solvent and for each of the other media a plot analogous to that shown in Fig. 2 for MeCN has been obtained. In general good linear free energy relationships were obtained, and no systematic deviation has been observed for any of the positions in the investigated substrates: benzene was simply considered as one of the substrates and an intercept was obtained. The results of the least squares treatment are shown in Table 2: the relative selectivity is given by the slope, correlation coefficients are high in all cases, and the intercepts are quite small.

No simple relation is apparent between the observed order of selectivity and physical or chemical properties (viscosity, dielectric constant, donicity number etc.),

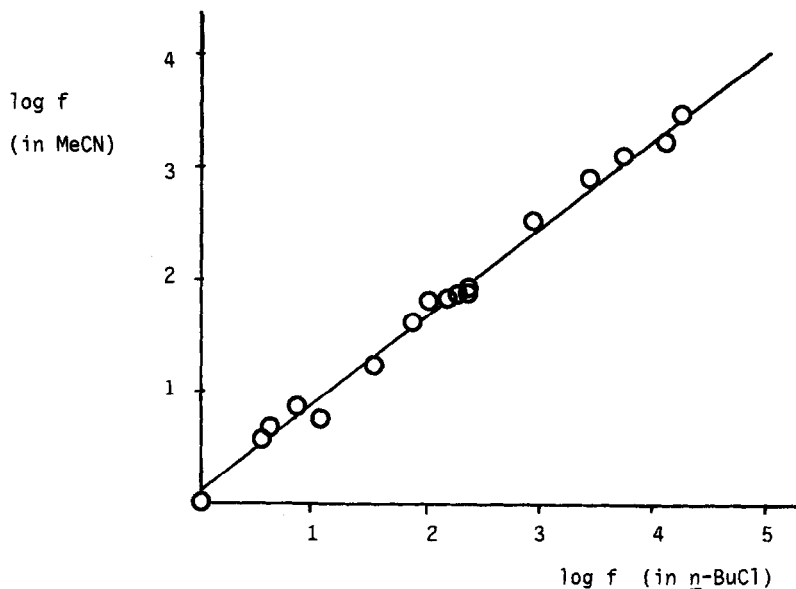


Fig. 2. Correlation between partial rate factors in the nitration reaction with Bu_4NNO_3 and TFAA in two different solvents. Values calculated from data in Table 1. The slope gives the relative selectivity.

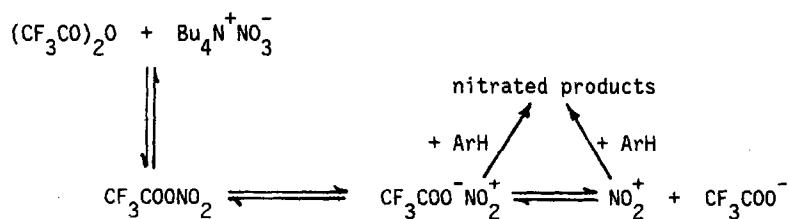
Table 2. The Effect of the Solvent, Relative to 1-Chlorobutane, on the Selectivity of the Electrophilic Aromatic Nitration with Bu_4NNO_3 - TFAA at 25 °C.^a

		Slope (Relative Selectivity)	Intercept	Correlation Coefficient
1	MeNO ₂	0.708	0.100	0.9924
2	MeCN	0.787	0.107	0.9960
3	Sulfolane	0.797	0.177	0.9936
4	CH ₂ ClCH ₂ Cl	0.886	0.050	0.9961
5	CH ₂ Cl ₂	0.947	0.025	0.9971
6	EtOAc	0.974	- 0.022	0.9957
7	<u>i</u> -PrBr	0.998	0.014	0.9993
8	<u>n</u> -BuCl	1.000	-	-
9	<u>n</u> -BuBr	1.003	- 0.006	0.9997
10	CHCl ₃	1.044	- 0.053	0.9987

a) Least squares treatment for log values of partial rate factors calculated from the data in Table 1. In all cases 18 points were used, including the point for benzene.

it appears nevertheless that distinctly higher selectivities are obtained in haloalkanes and EtOAc than in dipolar aprotic solvents. Ionic electrophiles can in principle react as free ions, ion pairs, or higher aggregates (some possible reaction paths are shown in Scheme I), and the contributes can be different in the various solvents.

SCHEME I



The fact that both free and associated ionic electrophiles can react is relevant if we want to interpret the slope values in Table 2 as the pure solvent effect on the selectivity of the same actual electrophilic species, and not merely as the composite effect of the solvent on the selectivity of the nitrating mixture Bu_4NNO_3 - TFAA. We note that in plots like Fig. 2 not only points for unhindered positions correlate, but also points for the attack to hindered positions, which should be handicapped by the bulkiness caused by association. So, the homogeneous selectivity picture obtained suggests that the same electrophile operates in the various solvents and the slopes in Table 2 can tentatively be regarded as the pure solvent effect on the selectivity of the same electrophilic species.¹⁸

The next step in our empirical approach to the selectivity of nitration of activated substrates in organic solvents is to compare data from different nitrating systems in the same solvent: clearly, in the absence of problems of macroscopic diffusion,¹⁹ the same selectivity picture is expected if the same electrophilic species acts in the two systems.

We have carried out the nitration reaction of benzene, toluene, *m*-xylene, anisole, and mesitylene with HNO_3 - Ac_2O in CH_2Cl_2 solvent at 25 °C,²⁰ in conditions similar to those used for the nitration with Bu_4NNO_3 - TFAA. The results were as follows, toluene: $k_{\text{rel}} = 59.1$, % *o*- = 59.4, % *m*- = 2.2, % *p*- = 38.4; *m*-xylene: $k_{\text{rel}} = 815$, % 2- = 14.5, % 4- = 85.5; anisole: $k_{\text{rel}} = 2610$, % *o*- = 76.7, % *p*- = 23.3; mesitylene: $k_{\text{rel}} = 4940$. The correlation between log values of partial rate factors for the two systems in the same solvent is shown in Fig. 3. Very interestingly, the slope is 1.00, the intercept very small (-0.033) and the correlation coefficient high (0.9954): this result strongly supports the operation of the same electrophilic species in the two systems. The electrophile can reasonably be thought to be the NO_2^+ ion, with no apparent difference in selectivity due to the presence of the CF_3COO^- or CH_3COO^- counter-ions.

Correlations as above are possible with data from the literature: for instance the data for the nitration with *N*-nitro-2,4,6-collidinium tetrafluoroborate in MeCN at 25 °C⁸ correlate with those from Table 1 in the same solvent (7 points, slope 1.06, intercept -0.036, correlation coefficient 0.9998). The slope slightly different from 1 can possibly reflect physical differences or be produced by experimental errors, it is however out of doubt that the linearity of the plot is very good, and no deviation is observed for hindered positions: this indicates that the

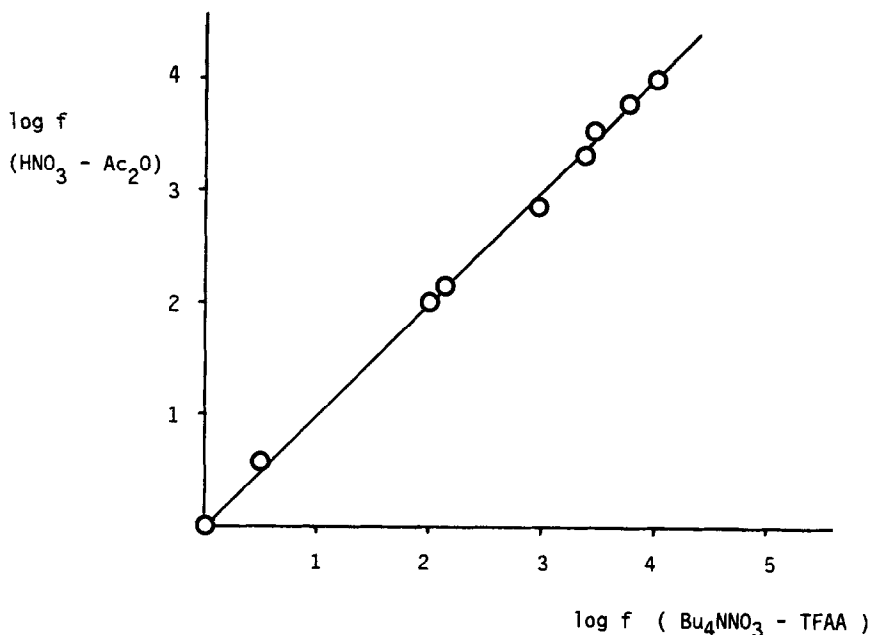


Fig. 3. Correlation between partial rate factors for aromatic nitration with two different nitrating systems in the same solvent (CH_2Cl_2) and at the same temperature (25°C).

Large N-nitro-2,4,6-collidinium ion is not the actual electrophilic species.

As these correlations are usually very good, deviating points can be easily singled out: for instance the data for the nitration with $\text{MeONO}_2\text{-BF}_3$ in MeNO_2 ⁹ correlate with our data in the same solvent (18 points, slope 1.01, intercept -0.080 , correlation coefficient 0.9860), but the linearity improves markedly on excluding the point for o-CH_3 , which is clearly out of the correlation (17 points, slope 1.05, intercept -0.116 , correlation coefficient 0.9960); the correlation is shown in Fig. 4.

Obviously, the above method can be extended to compare the selectivity of different nitrating systems in different media, and good correlations are observed for several nitration reactions in organic solvents: a more complete analysis will be given in due time.

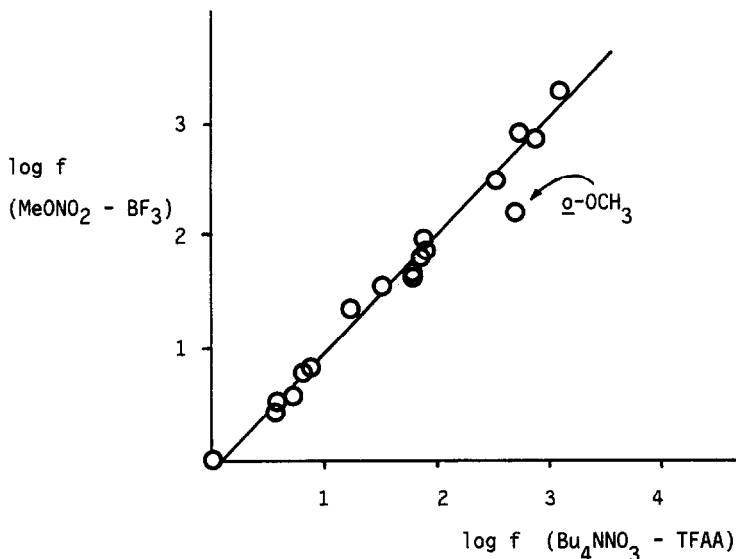


Fig. 4. Correlation between partial rate factors with two different nitrating systems in MeCN at 25 °C: special effects must operate for the attack ortho to $-OCH_3$, either in the $MeONO_2 - BF_3$ ⁹ or in the $Bu_4NNO_3 - TFAA$ system.

CONCLUDING REMARKS

In order to properly compare the reactivity or the selectivity of different reagents, the values in the same solvent should be available: this seems obvious in general in physical organic chemistry, but does not seem to have been a leading criterion in the study of electrophilic aromatic nitration of activated substrates in organic media. The effects of the solvent are now shown to be important, and can account for a large part of the differences in selectivity observed with different nitrating systems.

Were a more or less extensive control by the diffusion, or anything else, the cause of the peculiar selectivity of aromatic nitration, in the systems we have investigated a significant substrate selectivity is still observed between anisole and mesitylene, and this behaviour is shared with a number of other nitrating systems. This body of data, although not fully consistent with that from well behaved electrophilic aromatic substitutions, is a fairly homogeneous one and is suitable for a quantitative treatment.

EXPERIMENTAL

Materials. A 45 theoretical plates Todd column was used to purify by fractional distillation benzene, toluene, ethylbenzene, anisole, *i*-propylbenzene, nitromethane, and sulfolane (under vacuum). EtOAc, CH₂ClCH₂Cl, and *m*-xylene (Erba RP), Bu₄NNO₃, and *t*-butylbenzene (Fluka purum) and TFAA (Fluka puriss.) were used as received. 1-Chlorobutane (Erba RP), 1-bromobutane (Fluka purum), and 2-bromopropane (Merck or Fluka purum) were either used as received or distilled and stored over anhydrous K₂CO₃. Acetonitrile was distilled from phosphorus pentoxide through a 50 cm Vigreux column. The same technique was used for CH₂Cl₂ and CHCl₃, after treatment with H₂SO₄, washing with water, and drying over anhydrous Na₂SO₄: CHCl₃ was used within a few hours after distillation.

Competitive Kinetic Experiments. These were carried out by adding dropwise through a syringe 0.1 mL of a solution of Bu₄NNO₃ (0.12 M) and TFAA (0.80 M) in a given solvent, to a stirred 0.50 mL solution of a pair of aromatics (both 1 M) in the same solvent at 25 °C. Both the preparation of the nitrating mixture and the nitration reaction were carried out in septum capped vessels.² The nitrated products were analyzed by glc as previously reported.² Direct injection was possible in all cases but for sulfolane solvent: in this case water was added and the reaction products were extracted with pentane.

Mononitro derivatives were obtained in 60-90% yield with respect to Bu₄NNO₃: in some cases the reaction was carried out with the stoichiometric amount of an aromatic substrate, and the incomplete conversion into products was checked to be paralleled by the presence of the unreacted starting substrate. The lowest conversions were obtained in 1-bromobutane and 2-bromopropane, namely in this cases the yield was found to depend on the batch of the solvent, nor did distillation improve the conversions. In general the selectivity was not influenced on changing the batch of the solvent: the data in Table 1 for solvents 7, 8, and 9 refer to commercial samples.

Only the peaks relative to the expected mononitro derivatives were observed in glc, but no particular care was put to detect small quantities of high boiling products.

As to the nitration reaction with HNO₃-Ac₂O in CH₂Cl₂, the procedure described by Stock and Young¹¹ was followed for the purification of the reagents and the preparation of the nitrating mixture. 0.12 mL of the nitrating mixture (0.1 M in HNO₃ and 0.15 M in Ac₂O) in CH₂Cl₂, were added under stirring to 0.50 mL of a CH₂Cl₂ solution of a pair of aromatics (both 1 M) at 25 °C, with the same procedure followed for the nitration with Bu₄NNO₃-TFAA.

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