Journal of Fluorine Chemistry, 66 (1994) 9–11

Preliminary Note

Ordering of electrophilic fluorinating reagents of the N−F class

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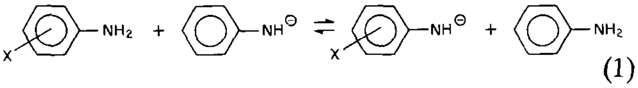
(Received December 12, 1992; accepted March 11, 1993)

Abstract

The order of the fluorinating ability of N−F reagents as assessed electrochemically is criticized. An alternative thermodynamic ordering, using calculated enthalpy couples [N(−I)/N(−III)] restricted to a closely related set of reagents, agrees with experimental observation. The cation's LUMO energy, rather than the localized electron density on nitrogen or fluorine, correlates with activity. A similar kinetic ordering would be expected if fluorination were controlled by N−F bond breaking because the reduction couples are also a measure of N−F bond dissociation energies.

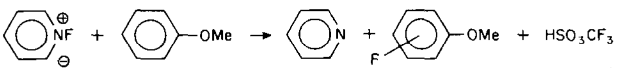
The recent ordering of chemical reactivity among *N*-fluoro reagents [1] is unsatisfactory for a number of reasons. Firstly, because of uncertainties in the electrochemical measurements and interpretation. The measured electroreductions were irreversible as well as being influenced by overpotentials on different electrode surfaces. This indicates reaction had occurred between the radical formed and the supporting electrolyte within the time scale of the voltage scan, thus lowering the peak reduction potentials E_p below the thermodynamic E^0 values. The dubious assumption made is that different radical reactions will always give a proportionate lowering of potentials. Secondly, true comparisons are difficult with such a divergent set of reagents. It is essential when making comparisons to compare like with like. For example, the general ordering of Lewis acid strengths can very with the choice of reference base unless sampling is restricted to a comparable set of acids. In the selection taken [1], some reagents were uncharged, others singly or doubly charged and even the counter anion was varied although it has been shown that reactivity varies with change of anion [2]. These factors affect solvation energies and can change E_p values just as changing the solvent does. Dipolar aprotic solvents, for example, considerably reduce rates [2]. The ordering in different solvents is only likely to remain invariant when E_p values are widely separated. The reported reproducibility of E_p values (± 0.05 V) does not allow several adjacent reagents to be differentiated (2 from 3; 4 from 5; 5 from 6; and 7 from 8 in ref. 1).

In a previous paper [3], a set of isoelectronic fluorinating reagents E_3AF_2, where A was a main group (V–VIII) element and E denoted a bonded or non-bonded electron pair, was ordered successfully using experimental or estimated enthalpies to obtain E_3AF_2/E_3A reduction couples. The *N*-fluoro compounds should be capable of similar ordering, although no experimental values are yet available. Gas-phase enthalpies were derived semi-empirically using the MNDO AM1 set of parameters. These were chosen since they most closely reproduce the experimental values for pyridine, the pyridine cation and anisole [4]. (Calc. values 32.0, 257.6 and -15.9 kcal mol^{-1} respectively, compared with experimental values 34.6, 264.9 and -17.3 kcal mol^{-1}.) It should be noted that only differences in AM1 values for closely related species are used in the ordering and this will, in general, reduce overall errors. Taft has demonstrated linear relations between ΔG values of couples in the gas phase and solution for proton transfers as well as linear free energy relations between gas-phase acidities and *ratios* of nucleophilic aromatic substitutions [5]. For example, aniline acidities, according to eqn. (1), were linearly related in the gas phase and in DMSO solution.



(1)

We can similarly compare fluorine transfer between substituted and unsubstituted pyridinium *N*-fluoro triflates in the gas phase and expect a correlation with the rates in solution. Their relative fluorinating ability has been determined [2] by timing their consumption when mixed with equimolar amounts of anisole in dichloromethane or ethane according to eqn. (2).



(2)

The subsequent neutralization of the pyridine formed by the strong triflic acid will be too rapid to influence the kinetics of the reaction depicted in eqn. (2). Hence,

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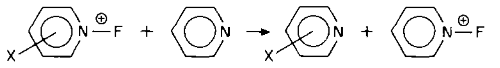
0022-1139/94/$07.00
SSDI 0022-1139(93)02929-9

TABLE 1. Calculated heats of formation and LUMO energies of *N*-fluoropyridine cations and the heats of the corresponding pyridines in kcal mol^{-1}

	Reduced form >N ΔH_f^0 value	Oxidised form >N−F$^+$ ΔH_f^0 value	Reduction couple $-\delta(\Delta H_f^0)$ value	−LUMO energy of oxidised form
1 pentafluoropyridine	−170.5	36.3	206.8	173.9
2 pentachloropyridine	8.7	204.9	196.2	154.0
3 2,6-difluoropyridine	−48.2	140.0	188.2	156.1
4 2,6-dichloropyridine	21.3	208.7	187.4	148.5
5 3,5-dichloropyridine	18.9	205.9	187.0	148.7
6 2,6-di(methylpicolinate)	−123	62.5	186.4	151.0
7 pyridine	31.9	209.2	177.3	143.9
8 2,6-dimethylpyridine	19.4	189.8	170.4	134.7
9 2,4,6-trimethylpyridine	11.5	178.8	167.3	131.4
10 piperidine	−22.0	148.6	180.6	123.1
11 quinuclidine	−8.4	161.5	169.9	117.8
N_2	11.2^a	275.0	263.8	200.2
FCN	−4.4	332.5	337.9	207.1

^{a}Calculated values for elements may differ from zero.

if constant terms are ignored, a reduction couple N(−I)/N(−III) is represented by $[\Delta H_f^0(\mathrm{py}) - \Delta H_f^0(\mathrm{pyF}^+)]$ and taking this couple as a reference level, the difference (δ) between couples is equivalent to an isodesmic fluorine transfer for which $\delta(\Delta S)$ is close to zero [6].


(3)

Consequently, a δ(ΔH couple) is a valid replacement for a δ(ΔG couple). Additionally, δ(ΔG solvation) in the non-polar solvents employed would be almost constant in the series.

Calculations (see Table 1) were also made with a minimum sized N_2F^+ cation and the recently prepared $F{-}C{\equiv}N{-}F^+$ [7], with which it is isoelectronic if F is counted as contributing one electron, as well as with a pair of saturated ring compounds.

Electronation of fluoro-immonium cations should be dependent on the relative levels of the cation LUMO with respect to the constant HOMO of anisole at −207.5 kcal mol^{-1}. Hence, one expects a relation between reagent reduction couples and cation LUMO values. This is illustrated in Fig. 1 where only the pentachloro compound deviates appreciably from the linear curve. The correlation $\Delta H_{\mathrm{couple}} = -[0.920(7)E_{\mathrm{LUMO}} + 54.7(3)]$ holds with a correlation coefficient of 0.998 if the chloro derivatives are excluded. (Possibly the AM1 parameters for chlorine have yet to be fully optimized.) A similar relation between reduction potentials and LUMO energies has been found previously for one-electron reductions of aromatic hydrocarbons [8]. In agreement with the contention that like must be compared with like, the values for saturated ring compounds lie well below the aromatic line. Thus even though the piperidine–pyridine or quinuclidine–dimethylpyridine pairs of reduction couples are closely matched, the reaction rates of the aromatics should be greater because of their more favourable acceptor levels. Similarly, the very powerful N_2F^+ and $FC{\equiv}NF^+$ pair are non-contiguous. The sequence of reduction couples within the aromatic set agrees with the experimental order of reactivity. Additional calculated values for 1, 3, 4 and 8, for which rates were not measured, fit in anticipated positions.

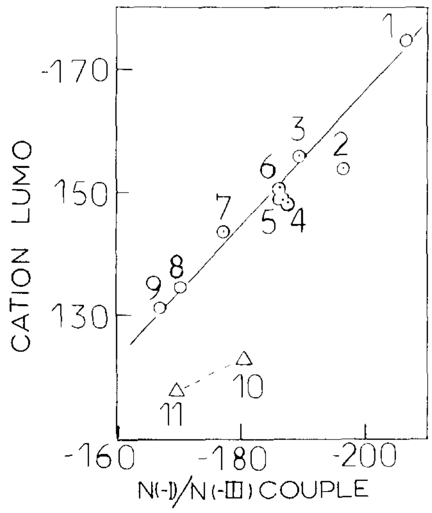


Fig. 1. Correlation between the enthalpies of reduction couples N(−I)/N(−III) and LUMOs in Kcal mol^{-1} for the fluoroimmonium ions listed in Table 1 (⊙, aromatic rings; △, saturated rings).

In view of the belief that fluorinating power increased as the electron density decreased at positive nitrogen sites [2], charge densities were calculated. Some typical values are collected in Table 2.

Admittedly, charge magnitudes vary with the orbital basis used in calculations, but any trends in a related

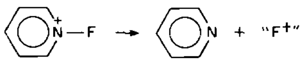
TABLE 2. Calculated distances and charges in cation and radical N−F bonds

Base	Cation*			Radical*		
	a	b	c	a	b	c
pentachloropyridine	1.36(5)	0.025	0.080	1.39(1)	0.040	−0.053
pyridine	1.36(3)	0.042	0.064	1.39(1)	0.017	−0.086
2,6-dimethylpyridine	1.36(4)	0.0164	0.0495	1.39(1)	0.024	−0.091
quinuclidine	1.39(2)	0.110	0.0003	1.46(9)	0.141	−0.237

*a = *d*(N−F); b = charge on N; c = charge on F.

series should be meaningful. It appears that fluorine is more positively charged than nitrogen in the aromatic cations and vice versa in the radicals where the N−F bond is stretched. Changes are more extreme with saturated species. There is no correlation between localized charges and fluorinating ability. Instead, the correlation is with the level of the delocalized acceptor MO as shown in Fig. 1.

Reduction couples relate to equilibria, yet they can still yield the correct kinetic ordering. This is explicable if the N−F bond-breaking process, however it occurs, controls the fluorination rate because the reduction couples are also a measure of bond strengths, viz.



The most negatively valued couple minimizes the positive dissociation energy.

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