

Regioselectivity and kinetics of fluorination of alkyl substituted phenols by *N*-fluoro-1,4-diazoniabicyclo[2.2.2]octane salt analogues

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Dedicated to Prof. Branko Stanovnik on the occasion of his 65th birthday

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Abstract

The 3,4-dialkylsubstituted phenols: 3,4-dimethylphenol, 5-indanol, and 5,6,7,8-tetrahydro-2-naphthol were used as target molecules for fluorination with the *N*-fluoro-1,4-diazoniabicyclo[2.2.2]octane salt analogues *Selectfluor*TM *F-TEDA* and *Accufluor*TM *NFTh*. 4-Fluoro-3,4-dialkylcyclohexa-2,5-dienone derivatives, as the result of an addition-elimination process, were the main, and 2-fluoro- and 6-fluoro-3,4-dialkylphenols derivatives resulting from a substitution reaction, the minor products of the fluorination process. The type of transformation was found to be independent of the structure of starting material and reagent, while these two parameters were important for the regioselectivity of the substitution reaction. The effect of the solvent on these reactions was evaluated, second order kinetics for the fluorination with *F-TEDA* in MeCN was established, rate constants k_2 were measured, and thermodynamic parameters for the transition state (ΔH^* , ΔS^* , and ΔG^*) determined. A reaction pathway postulating a SET process as the key step was proposed.

Keywords: Phenols, fluorination, kinetics, *Selectfluor*TM, *Accufluor*TM

Introduction

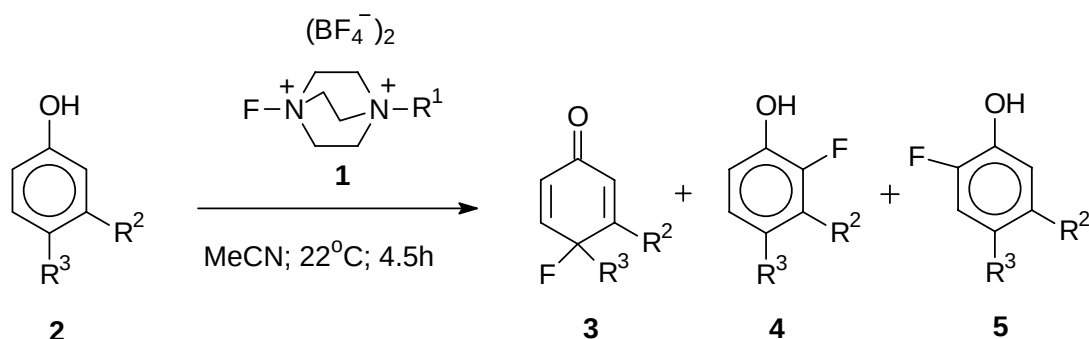
The introduction, followed very soon after by the broad synthetic application, of organic molecules incorporating reactive a *N*-F bond as versatile, site-selective and mild fluorinating reagents¹ represents one of the most important break-throughs in the last decade, reviving a strong impetus to related areas of chemistry, which are of considerable general interest to the basic and applied research community.² Very soon after their promotion,³ derivatives of *N*-

fluoro-1,4-diazoniabicyclo[2.2.2]octane salts became one of the most popular groups of these compounds, particularly 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (*Selectfluor*TM F-TEDA **1a**) which is actually one of the most often used site-selective fluorinating reagent. Its 1-fluoro-4-hydroxy- (*Accufluor*TM NFTh, **1b**) or 1,4-difluoro-substituted analogues, mainly due to their higher cost, achieved a lower commercial success. As well as being versatile fluorine atom transfer reagents, *N-F* compounds are also moderate to strong oxidants,⁴ and F-TEDA and NFTh are the strongest among them.⁵ Therefore we can expect a certain decrease in the selectivity of their reactions with target molecules bearing oxidisable functional groups or heteroatoms. Hydroxy groups bonded to an aromatic ring conveys a great deal of potential fluorofunctionalisation/oxidation competitive dualism and can represent a considerable selectivity diminishing factor, so that this issue still calls for further research. In our continuing interest in the reactions of *N-F* compounds with phenols⁶ we now report further investigations of the reactions of alkyl substituted phenols with *Selectfluor*TM F-TEDA and *Accufluor*TM NFTh.

Results and Discussion

3,4-Dialkyl substituted phenols have often been used as target molecules for evaluation and comparative characterisation of reagents and methods for halogenation of aromatic molecules. For this purpose 3,4-dimethyl phenol (**2a**), 5-indanol (**2b**) and 5,6,7,8-tetrahydro-2-naphthol (**2c**) are the most convenient tools, already used by Mills and Nixon in 1930 in their elaboration of the nonequivalency of two *ortho* positions for electrophilic substitution,⁷ known as the Mills-Nixon effect. The same targets were used in investigations of the bromination of phenols with elemental bromine,⁸ chlorination with chlorine^{9a} or SbCl₅,^{9b, 9c} and oxidative fluorination with an HF/pyridine mixture using PbO₂^{10a} or phenyliodo(III) bis(trifluoroacetate)^{10b} as oxidants.

In a typical experiment we stirred a solution of starting phenol **2** and fluorinating reagent **1** in acetonitrile at room temperature for 4.5 hours and after analysis of the crude reaction mixture obtained, established that the starting material was almost quantitatively transformed to three fluorinated products. The main product was identified as the 4-fluoro functionalised derivative of substituted cyclohexa-2,5-dienone **3**, while the minor two were recognised as fluoro substituted phenols bearing a fluorine atom bonded at *ortho* positions 2 and 6. From the relative distribution of the products of these reactions (**Table 1**), we can conclude that the most electron-rich positions of target molecules **2** were fluorofunctionalised and that *para* attack was considerably predominant over *ortho* one. The addition-elimination process, forming 4-fluoro-3,4-dialkyl-cyclohexa-2,5-dienone derivatives **3a-c**, was in these cases found to be much more pronounced than the substitution process resulting in 2-fluoro (**4a-c**) and 6-fluoro-3,4-dialkylphenols (**5a-c**).

Table 1. Fluorination of 3,4-dialkyl-substituted phenols with derivatives of *N*-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)^{a)}

2	Relative ratio between types of transformations (3 : 4 + 5) ^{b)}		Regioselectivity of the substitution (4 : 5)	
	F-TEDA	NFTh	F-TEDA	NFTh
2a 	85 : 15	84 : 16	1 : 2	1 : 2
2b 	85 : 15	84 : 16	1 : 6	1 : 3
2c 	85 : 15	88 : 12	2 : 1	3 : 1

^{a)} **1a**: $\text{R}^1 = \text{CH}_2\text{Cl}$; *Selectfluor*TM *F-TEDA*; **1b**: $\text{R}^1 = \text{OH}$; *Accufluor*TM *NFTh*. ^{b)} Determined from the ^{19}F NMR spectra of the crude reaction mixture; overall yield of fluorinated products (93-98%) was determined using octafluoronaphthalene (OFN) as internal standard.

The structure of the target phenols **2a-c**, as well as of the fluorinating reagents **1a,b**, has no effect on the type of the transformation, while these two parameters play important roles in the course of the substitution process. In the case of 3,4-dimethylphenol **2a** the ratio between 6- and 2-fluorination was about two, in 5-indanol **2b** this ratio was even higher, but in the case of 5,6,7,8-tetrahydro-2-naphthol **2c** the opposite regioselectivity was observed and 2-fluoro derivative **4a** found as the main product of the substitution reaction. These observations are very

similar to those established for the bromination of dialkyl substituted phenols,^{8a} and are in agreement with the relative reactivity expressed by partial rate factors for electrophilic displacement at both positions.¹²

Table 2. Effect of the solvent on the fluorination^{a)} of 3,4-dimethylphenol **2a** with F-TEDA and NFTh

Solvent	Relative ratio between types of transformation ^{b)} (3a : 4a + 5a)		Overall yield (%) ^{c)} 3a + 4a + 5a	
	F-TEDA	NFTh	F-TEDA	NFTh
MeCN	85 : 15	84 : 16	96	93
MeCN/MeOH 9.5 : 0.5	85 : 15	84 : 16	81	80
8 : 2	76 : 16 ^{d)}	82 : 18	75	75
7 : 3	72 : 17	79 : 21	75	62
4 : 6	52 : 20	59 : 31	49	47
MeOH	/	56 : 26	0	52
MeCN/H ₂ O 9 : 1	76 : 24	77 : 23	70	75
1 : 1	66 : 34	65 : 35	23	32
MeCN/CH ₂ Cl ₂ 9 : 1	81 : 19	82 : 18	90	80
7 : 3	80 : 20	82 : 18	79	47
4 : 6	75 : 25	75 : 25	17	13
CH ₂ Cl ₂	/	/	0	0
CF ₃ CH ₂ OH	/	/	0	0
MeO(CH ₂) ₂ OH	85 : 15	79 : 21	60	75

^{a)} Standard reaction conditions: 1 mmol of **2a**, 1 mmol of **1**, 10 mL of solvent, 22°C, 4.5 h. ^{b)} Determined from the ¹⁹F NMR spectra of the crude reaction mixture. ^{c)} Determined from the ¹⁹F NMR spectra of the crude reaction mixture using OFN as internal standard and calculated to starting material. ^{d)} Undefined product ($\delta F = -163 \text{ ppm(m)}$) started to form.

We further studied the effect of the solvent on the fluorination reactions and the data obtained with 3,4-dimethylphenol **2a** as the target are collected in **Table 2**. It is evident from these data that neither protic nor non-polar solvents do not stimulate the fluorination process. The relative amounts of fluorinated 3,4-dimethylphenols **4a** and **5a** increased with increasing protic character of the solvent and with decrease in its polarity, but the overall yield of

fluorinated products dropped considerably. Since *F-TEDA* and *NFTh* are less soluble in these solvents than in acetonitrile, this finding seems to be reasonable. On the other hand, we did not observe the formation of 4-hydroxy or 4-alkoxy substituted derivatives of 3,4-dimethylcyclohexa-2,5-dienone as a result of the attack of an external nucleophile, as was the case when 2,4,6-trialkyl substituted phenols^{6d, 6e} were used as starting molecules.

We further investigated the kinetics of these transformations and established that in the case of the use of *F-TEDA* as reagent the reaction rates obey the simple second-order rate equation

$$d[\text{F-TEDA}]/dt = k_2[\text{F-TEDA}]x[\text{phenol } \mathbf{2}] \quad (1)$$

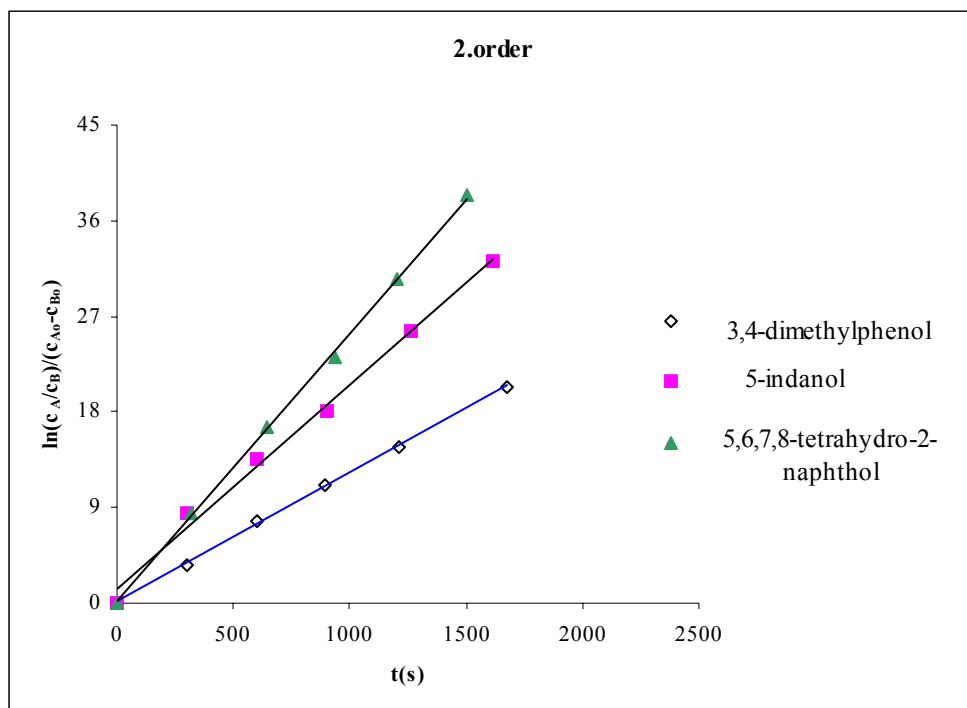
The second-order rate constants, measured by following the consumption of *F-TEDA* by iodometric titration, are collected in **Table 3** and **Table 4** and we can see that the structure of starting phenol **2** has a considerable effect on the reaction rates. 5-Indanol **2b** reacts 1.6 times faster than its acyclic analogue **2a**, while additional acceleration of the reaction was observed in the case of 5,6,7,8-tetrahydro-2-naphthol **2c** which reacts two times faster than **2a**. The thermodynamic parameters for the transition state of the reaction collected in **Table 4** are also instructive. The energies of activation ΔH^* for the fluorination of 3,4-dimethylphenol **2a** and of 5-indanol have almost the same value, while ΔH^* for 5,6,7,8-tetrahydro-2-naphthol **2c** is 4 kJ/mol lower. This difference in the activation barrier obviously can be attributed to the activation entropy ΔS^* which was found to have a negative sign but its lowest numerical value for the fluorination of 5-indanol **2b** and its highest for the transformation of 5,6,7,8-tetrahydro-2-naphthol **2c**. A reasonable explanation for this fact would be that in the case of 5-indanol strain between the aromatic and acyclic rings caused a lower degree of order in the activation complex in comparison with 5,6,7,8-tetrahydro-2-naphthol **2c**, where the more flexible six-membered ring releases these tensions. As the consequence of all this is that the free energy of activation ΔG^* has almost the same value for all three reactions.

The reaction pathway for the transformations of phenols with *N*-fluoro-1,4-diazoniabicyclo[2.2.2]octane salts analogues has been elaborated and discussed in our previous work.^{6d, 6e} We believe that in the case of the fluorination of 3,4-dialkyl substituted phenols **2** with *F-TEDA* or *NFTh* a single electron transfer (SET) reaction pathway is also the most likely reaction channel through which phenols **2** are transformed to products **3**, **4**, and **5**, with **1** and the primarily formed cation radical species further transforming to cationic species, being the reactive intermediates involved in these transformations (**Scheme**).

Table 3. Effect of the structure of 3,4-dialkyl-substituted phenols **2a-c** on the rate of fluorination with *F-TEDA*^{a)}

Phenol 2	k_2 (L / mol s)	$k_{\text{rel}}=k/k_{\mathbf{2a}}$
3,4-Dimethylphenol 2a	1.21×10^{-2}	1.0

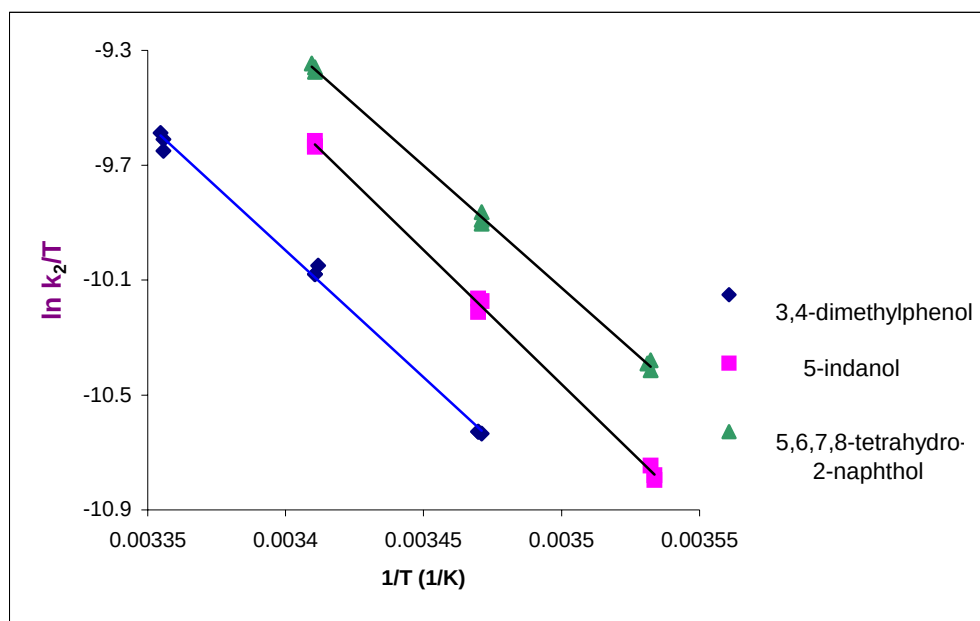
5-Indanol 2b	1.93×10^{-2}	1.6
5,6,7,8-Tetrahydro-2-naphthol 2c	2.53×10^{-2}	2.1

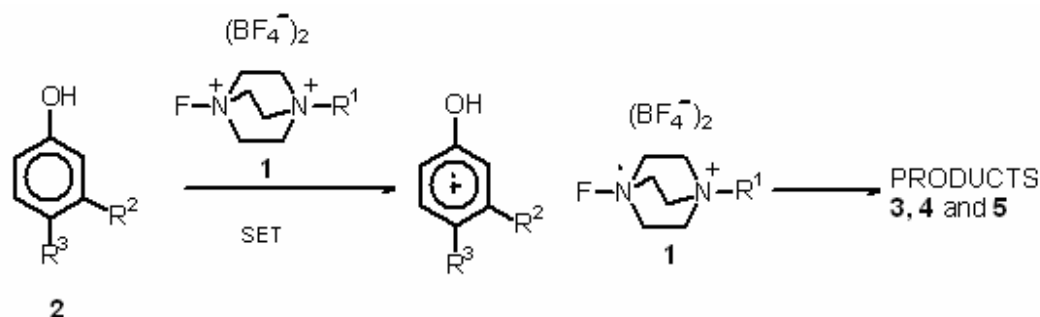


a) Solvent: MeCN; T=20.1°C; $C_{\text{phenol}} = 2 \times 10^{-2}$ mol/L.

Table 4. Thermodynamic parameters for the transition state for the fluorination of 3,4-dialkyl-substituted phenols **2a-c** with *F-TEDA* in MeCN

Phenol 2a-c	T (°C)	k_2 (L/mol s)	ΔH^* (kJ/mol)	ΔS^* (J/K mol)	ΔG^* (kJ/mol)
3,4-Dimethylphenol 2a	15	6.9×10^{-3}	73.8	-29.8	82.4
	20	1.2×10^{-2}			
	25	2.0×10^{-2}			
5-Indanol 2b	10	5.9×10^{-3}	74.1	-23.4	81.0
	15	1.1×10^{-2}			
	20	1.9×10^{-2}			
	10	8.7×10^{-3}			
5,6,7,8-Tetrahydro-2-naphthol 2c	15	1.5×10^{-2}	70.0	-36.3	81.0
	20	2.5×10^{-2}			





Scheme

Experimental Section

Materials. 1-Fluoro-4-chloromethyl-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (1a, *Selectfluor*TM *F-TEDA*) and 1-fluoro-4-hydroxy-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (1b, *Accufluor*TM *NFTh*, 50% w/w on alumina) were obtained from commercial sources, and for synthetic application used as received. For kinetic measurements *F-TEDA* and *NFTh* were crystallised from an acetonitrile-methanol mixture and dried under reduced pressure before use. 3,4-Dimethylphenol (2a), 5-indanol (2b) and 5,6,7,8-tetrahydro-2-naphthol (2c) from commercial sources were purified by crystallisation, acetonitrile was purified by distillation and stored over molecular sieves. KI and a standard solution of Na₂S₂O₃ from commercial sources were used as received. ¹H and ¹⁹F-NMR spectra were obtained at 60 MHz for proton and 56.4 MHz for fluorine resonance in CDCl₃ as solvent, and chemical shifts expressed in ppm from TMS or CFC1₃ as internal standards.

Fluorination of 3,4-dialkyl-substituted phenols 2a-c with *F-TEDA* or *NFTh*

To a solution of 1 mmol of substrate **2** in solvent (10 mL), 0.354 g (1 mmol) of *F-TEDA* or 0.640 g (1 mmol) *NFTh* was added and the reaction mixture stirred at 20°C for 4.5 hours. The solvent was removed under reduced pressure, the crude reaction mixture dissolved in CH₂Cl₂ (40 mL), and insoluble material filtered off. The solution was then washed with water (40 mL), dried over Na₂SO₄, and the solvent evaporated. The isolated crude reaction mixtures were analysed by ¹H and ¹⁹F-NMR, the amount of fluorinated products determined using octafluoronaphthalene as internal standard, and pure products obtained after separation by TLC (SiO₂, CH₂Cl₂/EtOH 50/1). The spectroscopic data for the products **3a**,^{6c} **3b**,^{10b} and **3c**^{10b} were in agreement with the literature, while products **4** and **5** were identified on the basis of differences in their ¹⁹F-NMR spectra, where compounds **5** are expressed as dd signal with well defined ³J_{FH5} and ⁴J_{FH2} coupling constants, while compounds **4** shows due to the correlation of fluorine atom with alkyl protons a multiplet signal for F-2.

2-Fluoro-3,4-dimethylphenol (4a) and 6-fluoro-3,4-dimethylphenol (5a). Yield 11% of an oily mixture of both isomers in 1:2 relative ratio. ^1H -NMR (60 MHz, CDCl_3): δ 2.1(s, 6H, CH_3), 6.6-7.1(m, 2H, ArH); ^{19}F nmr(54.6 MHz, CDCl_3): **4a**: δ -147.3(m) and **5a**: δ -148.0(dd, $^3J_{\text{FH5}}=11\text{Hz}$, $^4J_{\text{FH2}}=9.5\text{Hz}$); MS: m/z calculated for $\text{C}_8\text{H}_9\text{FO}$: 140.0637, measured: 140.0644; m/z: 140(M^+ , 95%), 125(100), 97(10), 91(24), 77(28).

4-Fluoro-5-indanol (4b) and 6-fluoro-5-indanol ¹¹ (5b). Yield 13% of an oily mixture of both isomers in 1:6 relative ratio. ^1H nmr (60 MHz, CDCl_3): δ 1.8-2.6(m, 2H), 2.6-3.1(m, 4H), 6.6-7.2(m, 2H); ^{19}F nmr(54.6 MHz, CDCl_3): **4b**: δ -148.2(m) and **5b**: δ -146.7(dd, $^3J_{\text{FH7}}=11.3\text{Hz}$, $^4J_{\text{FH4}}=8.5\text{Hz}$); MS: m/z calculated for $\text{C}_9\text{H}_9\text{FO}$: 152.0637, measured: 152.0643; m/z: 152(M^+ , 97%), 151(100), 133(53), 123(7), 103(32), 86(38), 84(61).

1-Fluoro-2-hydroxy-5,6,7,8-tetrahydronaphthalene (4c) and 3-fluoro-2-hydroxy-5,6,7,8-tetrahydronaphthalene (5c). Yield 12% of an oily mixture of both isomers in 2:1 relative ratio. ^1H nmr (60 MHz, CDCl_3): δ 1.6-2.1(m, 4H), 2.3-3.0(m, 4H), 6.5-7.0(m, 2H); ^{19}F NMR (54.6 MHz, CDCl_3): **4b**: δ -149.5(m) and **5b**: δ -147.8(dd, $^3J_{\text{FH4}}=18\text{Hz}$, $^4J_{\text{FH1}}=15\text{Hz}$);); MS: m/z calculated for); MS: m/z calculated for $\text{C}_{10}\text{H}_{11}\text{FO}$: 166.0794, measured: 166.0798; m/z: 166(M^+ , 75%), 138(100), 125(25), 120(13), 109(16).

Determination of reaction order and rate constants for reactions of hindered phenols with F-TEDA

Various amounts (0.9 mmol, 1.2 mmol and 1.5 mmol) of starting phenols were dissolved in 40 ml of acetonitrile thermostatted at 15°C . To each solution 0.6 mmol F-TEDA dissolved in 20 ml of acetonitrile thermostatted at 15°C was added and the reaction mixtures further stirred at 15°C . The progress of consumption of F-TEDA was monitored by iodometric titration. At different time intervals aliquots of 10 ml were pumped off from the thermostatted reaction mixtures, treated with 20 ml of 0.02 M KI and the liberated iodine titrated with 0.05 M $\text{Na}_2\text{S}_2\text{O}_3$. The consumption of F-TEDA followed a simple second order rate equation (1) and the second-order rate constants (k_2) collected in **Table 3** were determined as the slope of the correlation plot (2), which always gave a straight line with a correlation coefficient higher than 0.98. In eq.2

$$\ln(c_{\text{B0}}c_{\text{A}}/c_{\text{A0}}c_{\text{B}})/(c_{\text{A0}} - c_{\text{B0}}) = k_2t \quad (2)$$

where c_{A0} and c_{B0} are the initial concentrations of the reagent (F-TEDA) and the substrate (phenol), respectively, and c_{A} and c_{B} are the concentrations of the reagent and substrate, respectively, after time t . The values for k_2 collected in **Table 3** and **Table 4** are averages from at least three measurements with no more than 3% relative error.

Determination of the thermodynamic parameters of the transition state for the reaction of hindered phenols with F-TEDA

Second order reaction constants (k_2) for the reactions of target phenols with F-TEDA at different reaction temperatures were measured as described above. The relation of k_2 with temperature derived from the Eyring equation

$$\ln(k_2/T) = \ln(k_B/h) + \Delta S^\ddagger/R - \Delta H^\ddagger/RT \quad (3)$$

was found to follow a straight line with a correlation coefficient better than 0.98. The free energy of activation $\Delta G^\ddagger$ was calculated from the relation $\Delta G^\ddagger = \Delta H^\ddagger - T\Delta S^\ddagger$.

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