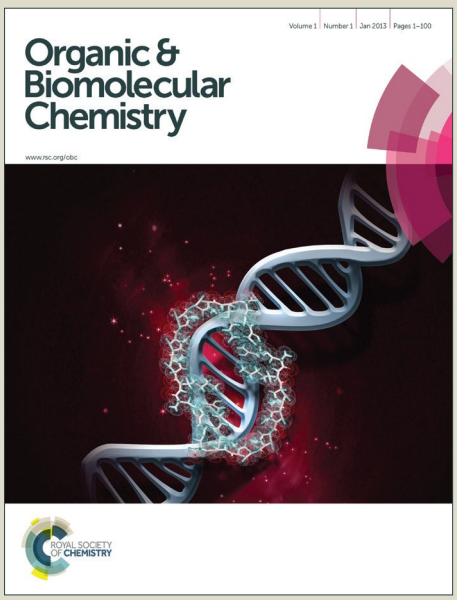
Organic & Biomolecular Chemistry

Accepted Manuscript



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ARTICLE

Electronic effects on the substitution reactions of benzhydrols and fluorenyl alcohols. Determination of mechanism and effects of antiaromaticity†

Cite this: DOI: 10.1039/x0xx00000x

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

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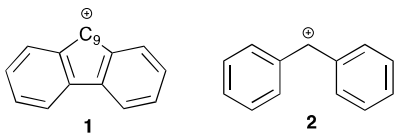
A range of substituted benzhydrols and fluorenols were prepared and subjected to acid catalysed methanolysis. Analysis of the rates of each of these processes showed correlation with Hammett σ+ parameters as is consistent with the significant build-up of positive charge adjacent to the ring. In combination with the similarity of the electronic susceptibility of the processes, these data suggest that both reactions proceed through a unimolecular rate-determining step. This shows that the effect of fusion of the phenyl systems (and hence potentially introducing an antiaromatic carbocation intermediate) is only to slow the rate of reaction rather than change the mechanism of the process.

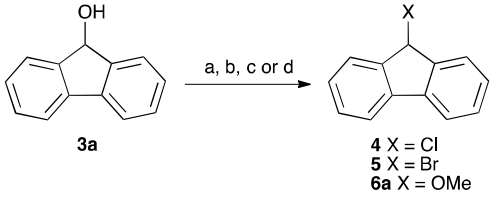
Introduction

Aromaticity is a well-known (and well exploited) concept in organic chemistry that was first named in 1855 by August Wilheim Hofmann.[1] In particular, aromatic systems have been noted to stabilise neighbouring carbocations through conjugation. Whilst such interactions of aromatic species are well-studied,[2-5] comparatively less attention has been paid to systems with antiaromatic character and their effects on reaction outcome.[6, 7] A well-known example of an antiaromatic system is the fluorenyl carbocation **1**.[8-10] Whilst there is obviously a requirement to define an appropriate reference system, the cation **1** has been shown to be substantially destabilised by antiaromaticity through both experimental[11] and computational means.[12] Whilst not exceptionally unstable, it is destabilised relative to the corresponding non-fused carbocation **2** by *ca*. 6 kcal mol^{-1}.[13] This leads to the central questions of this study, namely what influence does the antiaromatic character of the fluorenyl carbocation have on the reactivity (and possible available mechanistic pathways) at the 9-position of the parent fluorene? Furthermore, what effects does the antiaromatic nature of the system have on the transmission of electronic effects throughout the molecule?



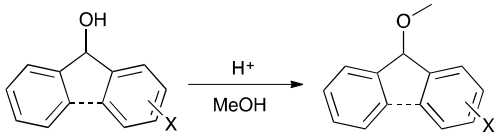
1 **2**

Substitution reactions of fluorenol **3a** provide a logical starting point given that many examples of such processes have been reported (Scheme 1).[14-18] While used synthetically, it is not immediately clear through which mechanism (either an S_N1 or an S_N2 process) the reactions proceed. Hence, this study sought to understand the mechanism through which the substitution of fluorenol derivatives proceed by considering acid catalysed methanolysis (Scheme 2). Through variation of the substituents on the fluorenols **3**, the electronic susceptibility of the process could be determined and compared to the equivalent requirement for the substituted benzhydrols **7**. This allows comment to be made on the mechanism of the reaction in each case and the effect of potentially proceeding through an anti-aromatic carbocation.



3a **4** X = Cl, **5** X = Br, **6a** X = OMe

Scheme 1 Some example substitution reactions of fluorenol **3a**. a) PBr_3;[14] b) $POCl_3$;[15] c) HCl, Δ;[16] d) MeOH, H^+, Δ.[17, 18]

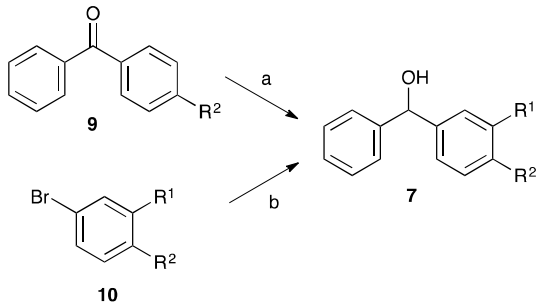


3 or 7 **6 or 8**

Scheme 2 The methanolysis of the fluorenols **3** and benzhydrols **7** to the corresponding methyl ethers **6** and **8**, respectively.

Results and discussion

Before the kinetic studies could be performed on the desired substituted benzhydrols **7** and fluorenols **3**, they needed to be synthesised. The substituted benzhydrols **7** were obtained either through a) reduction of the appropriate benzophenones **9a** and **9b**, which were commercially available, with lithium aluminium hydride (to give the unsubstituted **7a** and the *p*-methylated **7b**) or b) the lithiation of an appropriate aryl bromide **10c-e** with ^{n}butyl lithium at -78ºC in tetrahydrofuran followed by nucleophilic addition to benzaldehyde (Scheme 3, Table 1). Product identification was achieved through ^{1}H NMR spectroscopy (taking particular note of the methine signals at δ *ca*. 6) and comparison of physical and spectral data with that reported.[19-25]



Scheme 3 The synthesis of the substituted benzhydrols **7**. a) $LiAlH_4$, THF, 0ºC; b) i) nBuLi, ii) benzaldehyde, THF, -78ºC to r.t.

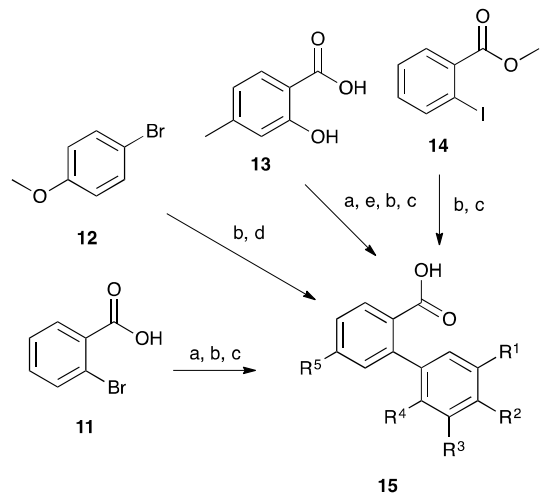
Table 1 The yields of the substituted benzhydrols **7** utilising the methodology above.

Compound	R^1	R^2	Yield (%)
	From substituted benzophenones **9**		
7a	H	H	95
7b	H	CH_3	79
	From substituted bromobenzenes **10**		
7c	CH_3	H	49
7d	H	CF_3	87
7e	OCH_3	H	53

The fluorenols **3** were prepared through the corresponding fluorenones, themselves generated from the appropriate biphenyl carboxylic acids. A range of commercially available starting materials **11-14** were used to access the required substituted biphenyl carboxylic acids **15** (Scheme 4, Table 2) with all pathways utilising Suzuki coupling chemistry.[26] Again, ^{1}H NMR spectroscopy and melting point comparisons were used to confirm the identity of the products,[27-30] with only the dimethylated species **15g** requiring full characterisation due to its novelty.

Having obtained the required substituted biphenyl benzoic acids **15**, Friedel-Crafts chemistry was used to cyclise the systems to the corresponding substituted fluorenones **16**, which were subsequently reduced with lithium aluminium hydride to give the desired fluorenols **3** (Scheme 5, Table 3). With the unsubstituted fluorenol **3a** being the only previously fully characterised species,[31, 32] all of the remaining substituted fluorenols **3** were fully characterised to ensure identity.

A further fluorenol **3i** was prepared through reaction of a substituent on a fluorenone. This species was prepared through oxidation of 3-methylfluorenone **16h** followed immediately by esterification in acidic methanol and subsequent selective reduction using sodium borohydride (Scheme 6).¢ Again, this species is novel and was fully characterised.



Scheme 4 The formation of the substituted biphenyl carboxylic acids **15**. a) cat. H_2SO_4, MeOH, Δ; b) $ArB(OH)_2$, SPhos, $Pd(OAc)_2$, Na_2CO_3, CH_3CN/H_2O, Δ; c) NaOH, EtOH, Δ, then acid work-up; d) $KMnO_4$, Py/H_2O, Δ; e) Tf_2O, NEt_3, DCM, 0ºC.

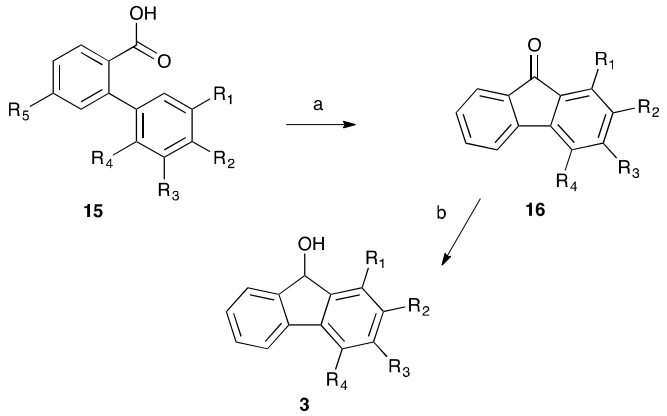
Table 2 The yields (over multiple steps) resulting from the synthetic protocols shown in Scheme 4.

No.	R^1	R^2	R^3	R^4	R^5	Yield (%)
	From 2-bromobenzoic acid **11**					
15c	H	CH_3	H	H	H	23
15d	H	CF_3	H	H	H	70
	From 4-bromoanisole **12**					
15e	H	OCH_3	H	H	H	92
	From 4-methylsalicylic acid **13**					
15f	H	H	H	H	CH_3	72
	From methyl 2-iodobenzoate **14**					
15g	CH_3	H	H	CH_3	H	78
15h	H	H	H	CH_3	H	50

With the necessary species in hand, kinetic experiments were carried out to determine the observed first order rate constant (k_{obs}) for the methanolysis of the benzhydrols **7**.$ Determined in a manner analogous to described previously using ^{1}H NMR spectroscopy,[33] the observed rate constant is a function of the extent of protonation of the alcohol and the acid concentration. As also detailed previously, variation in the former can be considered negligible and all changes in the observed rate constant attributed to changes in the substrate affecting the stabilisation of the intermediate carbocation.

The methanolysis of benzhydrol **7a** has been reported previously at 23.8°C, with an observed rate constant of 6.16(6) x 10^{-5} s^{-1}.[33] The same process was undertaken with the series of substituted benzhydrols **7b-7e** and the rate constants are shown in Table 4 (which is ordered by the electronic nature of

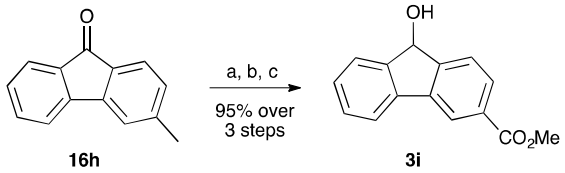
the substituent). Note that for the case with the extremely electron-withdrawing substituent (the trifluoromethyl derivative **7e**), as the reaction was very slow, it was carried out in a temperature controlled water bath rather than *in situ* in the spectrometer.



Scheme 5 The synthesis of the reactive fluorenols **3** through Friedel-Crafts ring closure and subsequent lithium aluminium hydride reduction. a) i) $SOCl_2$, ii) $AlCl_3$, DCM, 0ºC; b) $LiAlH_4$, THF, 0ºC.

Table 3 The multi-step yields obtained from the synthesis of the fluorenols **3**. €

No.	R_1	R_2	R_3	R_4	Yield (%)
3a	H	H	H	H	99
3b	H	H	CH_3	H	89
3c	H	CH_3	H	H	13
3d	H	CF_3	H	H	31
3e	H	OCH_3	H	H	74
3g	CH_3	H	H	CH_3	91
3h	H	H	H	CH_3	87



Scheme 6 The conversion of 3-methylfluorenone **16h** to the methyl ester **3i**. a) $KMnO_4$, Py/H_2O, Δ; b) cat. H_2SO_4, MeOH, Δ; c) $NaBH_4$, MeOH, 0ºC.

Table 4 The observed rate constant for the methanolysis of each of the alcohols **7a-e** in acidic methanol at 23.8°C. Uncertainties are reported as half the range of triplicate experiments.

Alcohol	k_{obs} / 10^{-5} s^{-1}
7b	142(16)
7c	14(3)
7a	6.16(0.6)[33]
7d	4(1)
7e	0.0206(0.0012)

As can be seen in the data presented in Table 4, there is a significant decrease in the rate constant with increasing electron-withdrawing ability. Whilst the Hammett plot of these data against σ values[34] gave a good correlation (R^2 = 0.974, Figure S1) unsurprisingly, given the anticipated significant build-up of positive charge as the reaction proceeds, the correlation improves significantly when σ^+ values[35] are used (R^2 = 0.999, Figure 1). This, in combination with the very large electronic susceptibility in this case (a reaction constant, ρ^+, of -4.15 ± 0.07), is consistent with a significant amount of charge build-up in the transition state as would be anticipated for a process that proceeds through an S_N1 mechanism. The good correlation across all of the substituents considered is also consistent with no change in mechanism across the range of substrates.

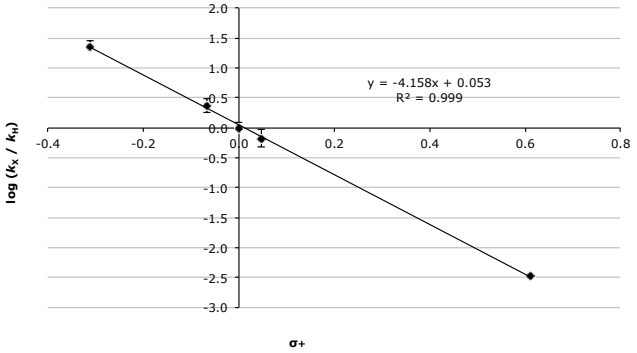


Figure 1 Hammett plot (using σ^+ values) for the methanolysis of the benzhydrols **7** at 23.8ºC with errors calculated through standard means.[36]

Initial studies on the corresponding fluorenols **3** under the same conditions as were used for the benzhydrols **7** showed that the fluorenols **3** did not react to any observable extent in a reasonable time frame. As such, the reactions were repeated at 60.0ºC where the reaction rates allowed more practical assessment of reaction progress (with half lives in the order of hours) to give the rate constants shown in Table 5 (once again, ordered by electronic nature of the substituent). It is worth noting that in comparison the methanolysis of benzhydrol **7a** proceeds with a rate constant of 5.44(30) x 10^{-3} s^{-1} under these conditions.

Table 5 The observed rate constant for the methanolysis of each of the alcohols **3** in acidic methanol at 60.0°C. Uncertainties are reported as half the range of triplicate experiments.€

Alcohol	k_{obs} / 10^{-5} s^{-1}
3g	348(20)
3b	56(11)
3h	11.7(0.6)
3c	5.73(0.23)
3a	3.14(0.30)
3e	2.36(0.24)
3i	0.0246(0.0025)
3d	0.0448(0.0020)

Once again, there is a clear trend in these data, with marked decreases in the rate constant on increasing the extent of electron withdrawing ability of the substituent. Quantification through a Hammett plot is more complicated in this case as

several assumptions must be made. In all cases, the effect of the substituents is assumed to be unaffected by the fusion to the adjacent ring; whilst a reasonable and necessary assumption, its limitations are demonstrated by comparing the rates of species **3h** and **3c**. Alcohol **3g** is further problematic as the effects of the two substituents is simply assumed to be additive (reasonable given they are both electron donating) whilst a substituent at the 1-position is assumed to have a sigma value the same as that at the 3-position.£

Even taking into account these complications, the Hammett analysis is fruitful. For the data presented in Table 5, using the Hammett σ values[34] gave a reasonable correlation ($R^2 = 0.949$, Figure S2) though, again, this improves significantly when σ^+ values[35] are used ($R^2 = 0.980$, Figure 2).

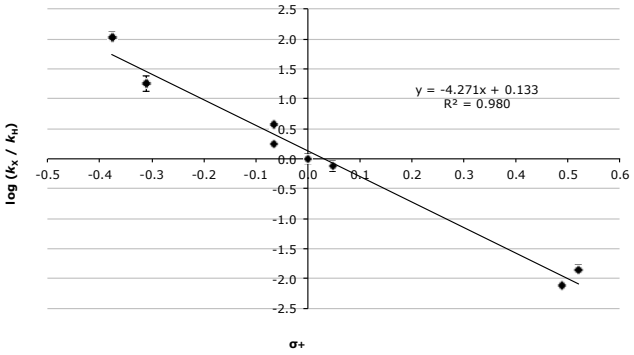


Figure 2 Hammett plot (using σ^+ values) for the methanolysis of the fluorenols **3** at 60.0ºC with errors calculated through standard means.[36]

There are several key points to take away from the correlation presented in Figure 2. Initially the fact that the correlation with σ^+ values, which represent the enhanced resonance properties of the substituents, is better than with σ values is consistent with significant carbocation character developing adjacent to the ring. Once again, this is supported by the magnitude and sign of the slope (-4.27 ± 0.25). Further, the linearity of the data indicates no change in mechanism over the range of species studied.

These data allow the effect of ring fusion of the benzhydrols **7** to give the fluorenols **3** on reactivity to be considered. The goodness of fit with enhanced resonance Hammett sigma parameters in the both cases, and the slopes of said correlations, is consistent with significant build-up of positive charge adjacent to the phenyl ring in the transition state for the fluorenols **3**. This is consistent with both reactions proceeding through an S_N1 mechanism.¥ The similarities in the electronic susceptibilities of the two processes (same given measurement uncertainties) shows that whilst the fusion of the carbon backbone may significantly decrease the overall ability of the system to stabilise the intermediate carbocation (as demonstrated by the relative rates of the two processes shown in Scheme 2 and summarised in Tables 1 and 2), it is has a very minor effect upon the extent to which the electronic nature of the substituents affects reaction outcome.

Conclusions

The above results demonstrate that whilst introducing anti-aromatic character into a carbocation intermediate may dramatically affect the rate of reaction, it does not necessarily change the mechanism of reaction where a viable alternative pathway is not available. Further, it demonstrates that the transmission of electronic effects in systems are comparable to those in aromatic systems. This has implications for the reactivity of larger polycyclic hydrocarbons with anti-aromatic character.

Experimental

All chemicals used were purchased from either Sigma-Aldrich, Alfa Aesar, Strem, Boron Molecular or Precious Metals Online and were used without further purification. Organic solvents used in synthesis were either used as received from Ajax Finechem or collected from a Pure Solv MD Solvent Purification System.

NMR spectroscopy was performed using either a Bruker Avance 300 (300.13 MHz, ^{1}H; 75.5 MHz, ^{13}C), an Avance III 400 (400.13 MHz, ^{1}H; 100.6 MHz, ^{13}C) with a Prodigy cryoprobe cppbbo, an Avance III 500 (500.13 MHz, ^{1}H; 125.7 MHz, ^{13}C) with a tbi probe or an Avance III 600 (600.13 MHz, ^{1}H; 150.9 MHz ^{13}C). NMR spectra were processed using the Bruker TOPSPIN 3.0 software.

Full synthetic procedures can be found in the ESI as per the reaction schemes shown throughout the Results and Discussion. The carboxylic acid intermediate **16g** as well as the alcohols **3b - 3i** had not been previously prepared so were fully characterised, whilst the remainder had physical and spectral data matching that reported in literature (see ESI for full details).

The corresponding methyl ethers (**6a-c** and **6e-h** and **8a-e**) were isolated after being treated with acidic methanol at reflux for 3 hours (full details of the preparation, along with appropriate characterisation, can be found in the ESI).

Kinetic analysis of the methanolysis of alcohols 3 and 7

A solution of sulfuric acid (98% w/w, 35 mg, 360 μmol) in deuterated methanol (0.6 mL) was generated. Of this, a portion (0.5 mL) was added to an NMR tube that contained the alcohol (28 μmol) being investigated. The reaction mixture was held at either 23.8ºC or 60 ºC in an NMR spectrometer or temperature controlled water bath and ^{1}H NMR spectra taken at appropriate intervals until at least three half lives had been measured. The extent of reaction at a given time was determined through comparing the integration due to a signal corresponding to the starting material relative to the integration of a signal due to the product ether (see ESI). This allowed calculation of observed first order rate constants for the methanolysis of the alcohols under these conditions. The kinetic analysis for each alcohol was carried out in triplicate.

Acknowledgements

SRDG acknowledges the support of the Australian government through the receipt of an Australian Postgraduate Award. JBH acknowledges financial support from the Australian Research Council Discovery Project Funding Scheme (Project DP130102331). The authors would like to acknowledge the NMR Facility within the Mark Wainwright Analytical Centre at the University of New South Wales for NMR support.

Notes and references

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† Electronic Supplementary Information (ESI) available: Hammett plots of the data presented in Tables 1 and 2 against σ values; Hammett plot of the data presented in Table 2 showing the effect of modifying the effective σ^+ value for the *ortho*-methyl substituent; general reduction of the ketones **9a,b** using lithium aluminium hydride; general reaction of benzaldehyde with *in situ* generated aryl lithium from the aryl bromides **10c**-e; general method for the esterification of benzoic acids; general Suzuki coupling to give methyl biphenyl benzoates; general deprotection of methyl benzoates; formation of the substituted biphenyl-2-carboxylic acids **15g,h**; preparation of 2-(4'-methoxy)benzoic acid **15e**; general method for the ring closure of the benzoic acids 15 to the fluorenones **16**; preparation of compounds **16i** and **3i**; general method for the formation of the fluorenols **3**; general method for the formation of the methyl ethers **6** and **8**; kinetic analysis, including all rate data, for the methanolysis of species **3** and **7**; ^{1}H and ^{13}C NMR spectra for all novel compounds. See DOI: 10.1039/b000000x/

$ In determining k_{obs}, no assumption is made on the order of the reaction. If the process is first order with respect to the protonated alcohol species, then $k_{obs} = k_1$, whilst if the process is bimolecular involving the methanol nucleophile, then $k_{obs} = k_2$[methanol] (the latter concentration term is constant). In either case, subsequent analysis allows determination of reaction order.

¢ Values for related process that proceed through an S_N1 reaction mechanism, such as the reaction of (diphenyl)methyl chlorides with alcohols, have reaction constants in range -2 to -5; the value depends on the exact nature of the reagents, along with the temperature and the solvent. For an early review in which this is shown, see the work of Jaffé.[37]

£ No attempt was made at more complicated analysis, such as that by Fujita and Nishioka,[38] though it should be noted that the field effects of a methyl substituent would result in the assumptions used here underestimating the electron donating effect of an *ortho*-methyl substituent. Increasing the electron donating effect (corresponding to decreasing the effective substituent constant) for alcohol **3h** does improve the correlation (Figure S3), with no significant effect on the observed reaction constant.

¥ It is also possible that one or both processes proceed through a bimolecular mechanism with an extremely 'open' or 'loose' transition state,[39] though this is considered the less likely of the two possibilities.

€ Due to the symmetry of the system (*i.e.* R_5 is equivalent to R_3 after ring closure), compound **3f** is the same as compound **3b** and is therefore not shown in the table.

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