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Reactivity of an electrophilic hypervalent iodine trifluoromethylation reagent with hydrogen phosphates—A mechanistic study

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ABSTRACT

The electrophilic trifluoromethylation of hydrogen phosphates with the reagent trifluoromethyl-1,3-dihydro-3,3-dimethyl-1,2-benziodoxole (**1**) was studied by means of initial rates determined for pseudo first order setups and subsequent Taft analysis of the calculated relative rates. A positive polar sensitivity factor, indicative of a negative charge forming during the rate-determining step, was found for the whole data set.

1. Introduction

Phosphates are naturally ubiquitous functional groups and are for example found in the backbones of DNA and RNA strands. Thus, they have been subjected to various modifications in order to enhance inherent properties such as the stability towards nucleases [1]. As we already reported the electrophilic trifluoromethylation of *S*-hydrogen phosphorothioates, bioisosters to phosphates, we also considered the direct conversion of hydrogen phosphates to trifluoromethyl phosphates with our reagent **1** (trifluoromethyl 1,3-dihydro-3,3-dimethyl-1,2-benziodoxole) in order to increase the lipophilicity of such functional groups [2,3]. With a pK_a of 3.15 in 80% ethanol, diethyl hydrogen phosphate is expected to be less acidic than the corresponding diethyl *S*-hydrogen phosphorothioate (pK_a = 2.88 in 80% 2-methoxyethanol) [4].[1] Thus, as we have conclusively shown that the activation of reagent **1** by protonation is a crucial factor in the reactivity towards nucleophiles, we expected hydrogen phosphates to react more slowly than *S*-hydrogen phosphorothioates [3,5].

2. Results and discussion

In order to probe the mechanism at work by means of the Taft equation a series of sterically and electronically diverse substrates were to be prepared [6]. Starting from phosphonates **2a–k**, prepared as previously reported [3], chlorophosphates **3a–k** were accessed in moderate yields ranging from 18% to 62% through oxidation at phosphorus by anhydrous $CuCl_2$ in THF and purified by means of high-vacuum distillation [7,8]. Unfortunately, the cyclohexyl derivative (**3g**) underwent pyrolytic decomposition during distillation such that the crude product had to be used in the subsequent step. Finally, hydrolysis of the chlorophosphates **3a–k** was achieved by treatment of a 1 M solution in THF with 1 M aqueous sodium hydroxide (Scheme 1).[2] The crude alkyl hydrogen phosphates (**4a–k**) were subsequently purified by dissolution in a sat. sodium bicarbonate solution, washing of the aqueous layer with CH_2Cl_2 followed by acidification with 1 M HCl and extraction of the pure products with CH_2Cl_2. As this method of purification proved to be highly efficient, it was found advantageous not to isolate the chlorophosphates but to directly react the crude materials in the final step.

Initially, the reactivity of reagent **1** towards diethyl hydrogen phosphate (**4b**) was studied showing that no reaction occurred at ambient temperature, hence corroborating that reagent **1** was activated to a lesser degree than observed for corresponding phosphorothioates. Monitoring of the reaction in various chlorinated solvents by means of pseudo 2D ^{19}F NMR experiments at

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[1] Direct comparison is not possible due to solvent effects. However, *O,O*-diethyl *S*-hydrogen phosphorodithioate has a reported pK_a value of 2.56 in 80% ethanol [4a]. Therefore, *O,O*-diethyl *S*-hydrogen phosphorothioate is expected to be more acidic in 80% ethanol than the corresponding hydrogen phosphate.

[2] *Caution:* Chlorophosphates are highly toxic!

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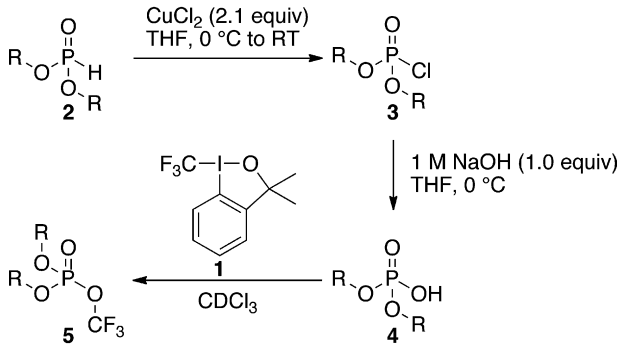


Scheme 1. Synthesis of dialkyl chlorophosphates and dialkyl hydrogen phosphates starting from dialkyl phosphonates.

40 °C selected chloroform to be used in further studies.[3] Additionally, screening of the optimal reagent–substrate ratio led to two key insights (Fig. 1). The maximum yield achieved is low and, more importantly, the concentration of reagent **1** decays faster than product is formed, thus indicating that significant side-reactions are operating. Further probing of the reaction mechanism by means of relative rates was not possible due to insufficient spectral resolution and due to the fact that relative rates determined at the beginning of the reaction varied significantly from those determined during its course. Therefore, initial rates for pseudo first order experiments (10 equiv. of substrate) were determined by means of ^{19}F NMR spectroscopy at 40 °C.[4] Every measurement was carried out twice to ensure reproducibility such that relative uncertainties of 13% to 18% were obtained for the relative rates k_R/k_{Me} and 0.9–4.8% for k_R/k_{Et}.

Fig. 2 depicts a Taft plot only considering inductive influences ($\delta = 0$). The analogous representation only considering steric influences can be found in the supporting information. In both cases the relative rate k_R/k_{Et} (using **4b** as a standard) and hence the modified Eq. (1) were used. The methyl derivative **4a** is not suited as a standard because its initial rate data could not be reproduced reliably enough. This is also corroborated by the direct comparison of the relative uncertainties obtained for the differently standardized relative rates (Table 1):

$$\log\left(\frac{k_R}{k_{Et}}\right) = \rho^*(\sigma_R^* - \sigma_{Et}^*) + \delta(E_{S,R} - E_{S,Et}) \quad (1)$$

Fig. 2 suggests a linear dependence for the region of $\sigma^*_{corr} \geq -0.03$ whereas the methyl derivative would not be taken into consideration. Furthermore, for $\sigma^*_{corr} < -0.03$ strong bending, whilst maintaining a positive slope, is observed. Whereas a change in the sign of the slope would indicate a change of mechanism or rate-determining step, gradual change in magnitude of the slope is pointing towards an equilibrium situation [9]. Multiple linear regression according to Eq. (1) neglecting the data obtained for compounds **4d** and **4g** yields $\log(k_R/k_{Et}) = (0.681 \pm 0.033)\sigma^*_{corr} + (0.095 \pm 0.008)\delta^*_{corr}$ with $R^2 = 0.99$, thus confirming the expected positive slope.[5,6] As the magnitude of ρ^* is <1 the reaction is found

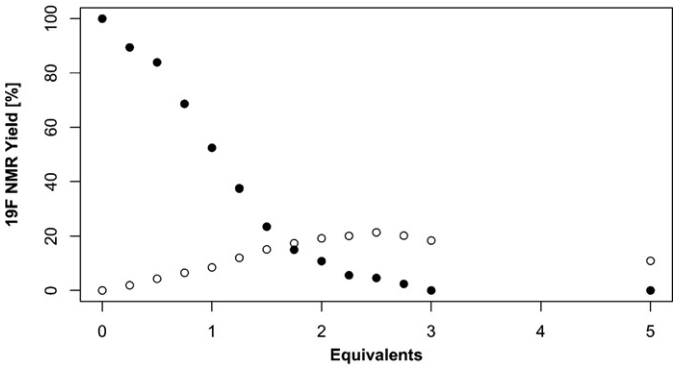


Fig. 1. Determination of the yield of diethyl trifluoromethyl phosphate (**5b**) (white dots) against the internal standard (α,α,α-trifluorotoluene, 1 equiv. relative to initial **1**) for reaction mixtures containing different initial diethyl hydrogen phosphate (**4b**) to reagent **1** ratios in $CDCl_3$ kept at 40 °C for 18 h shows a maximum of 21% at 2.5 equiv. Consumption of reagent **1** demarked by black dots.

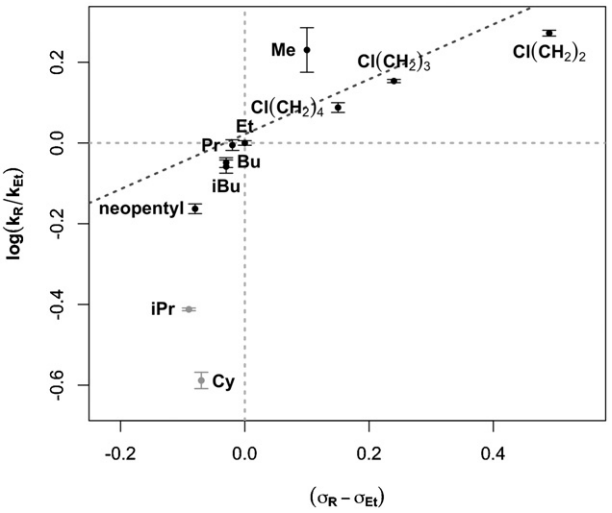


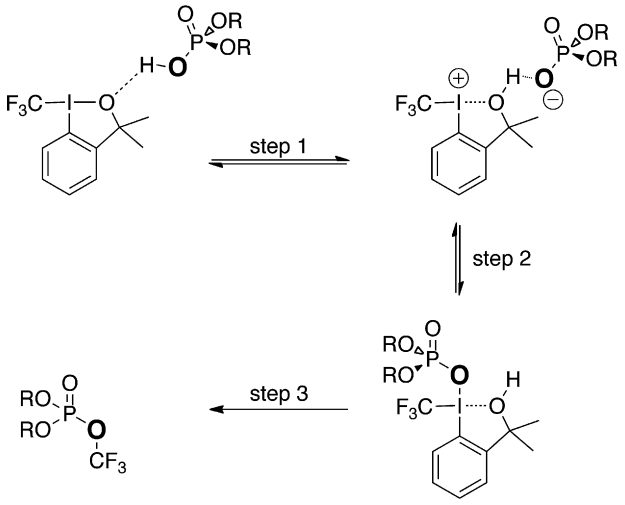
Fig. 2. A Taft plot with a projection of the plane defined by Eq. (1) for $\delta = 0$ is given. Data points in grey were not considered in the regressional analysis. For $\sigma^*_{corr} < -0.03$ strong bending is observed. For $\sigma^*_{corr} < -0.03$ a linear relationship is suggested. For all regions, however, a positive slope is found indicating the formation of negative charge during the rate-determining step.

Table 1
Summary of yields obtained for the substrate syntheses and the trifluoromethylation (Scheme 1), as well as of the differently standardized relative rates $k_{R/Me}$ and $k_{R/Et}$.

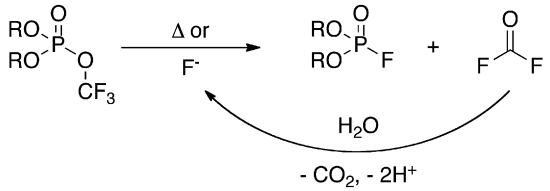
Entry	R	**3** (%)	**4** (%)	**5** (%)[a]	$k_{R/Me}$ (%)[b]	$k_{R/Et}$ (%)[b]
a	Me	–[c]	46	22	1.00 (17.9)	1.70 (12.7)
b	Et	–[c]	92	32	0.59 (12.7)	1.00 (1.3)
c	Pr	45	74	37	0.58 (13.0)	0.99 (3.0)
d	^{i}Pr	31	73	27	0.23 (12.7)	0.39 (0.9)
e	Bu	45	46	36	0.53 (12.9)	0.89 (2.8)
f	^{i}Bu	62	75	38	0.51 (13.2)	0.87 (3.7)
g	Cy	–[d]	23[e]	44	0.15 (13.5)	0.26 (4.8)
h	Neopentyl	18	81	43	0.40 (12.9)	0.69 (2.8)
i	$Cl(CH_2)_2$	38	70	28	1.10 (12.7)	1.87 (1.6)
j	$Cl(CH_2)_3$	26	75	21	0.84 (12.7)	1.42 (0.9)
k	$Cl(CH_2)_4$	21	85	30	0.72 (12.9)	1.22 (2.8)

[a] Determined by ^{19}F NMR with α,α,α-trifluorotoluene as internal standard for mixtures of 10:1 of substrate to reagent.
[b] In parentheses, relative uncertainties calculated as $\sigma_{R/Me}/k_{R/Me}$ and $\sigma_{R/Et}/k_{R/Et}$.
[c] Commercially available.
[d] Could not be isolated in a pure form due to thermolysis during distillation.
[e] Calculated over two steps starting from dicyclohexyl phosphonate (**2g**).

[3] Results of the monitoring experiments as well as a description of the pseudo 2D experiment acquisition routine are provided in the supporting information.
[4] As initial rates are highly sensitive to variations in concentration a pseudo first order setup was chosen in order to minimize errors and increase reproducibility.
[5] **4d** and **4g** were neglected as strong bending is observed for $\sigma^*_{corr} < -0.03$. **4h** is similar enough to the rest of the data such that it can be considered a part of the regression as inspection of Fig. 2 indicates. For **4k** no steric parameter E_S was available, thus it was approximated using the same value as for **4e** (Bu).
[6] The multiple linear regression was performed using R 2.11.1 GUI 1.34 Leopard build 32-bit (5589). For all calculations the preferred σ^* values reported in Ref. [10] were used. For compound **4k** the σ^* value was calculated according to: A. Brandstorm, J. Chem. Soc., Perkin Trans. 2 (1999) 1855.



Scheme 2. Proposed three-step mechanism accounting for the positive slope found (Fig. 2) and the non-linearity by postulating an initial proton-transfer equilibrium resulting in the development of a negative charge on the key oxygen (highlighted).



Scheme 3. Proposed initial thermal decomposition of the product is followed by autocatalytic fluoride-promoted decomposition yielding the corresponding fluorophosphates.

to be only slightly sensitive towards inductive effects. Moreover, the positive slope points to the formation of a negative charge during the RDS. With a steric sensitivity factor of $\delta = 0.095 \pm 0.008$ the reaction is found to be slightly accelerated if larger substituents are used. Based on these observations the following mechanistic interpretation is proposed (Scheme 2).

The initial proton-transfer equilibrium constituting the RDS is followed by a nucleophilic attack of the substrate on the iodonium core to yield the final intermediate that undergoes reductive elimination to furnish the desired dialkyl trifluoromethyl phosphates. Variation of the inductive properties of the substituent *R* significantly influences the acid strength of the hydrogen phosphates and thus the proposed initial equilibrium (Scheme 2, step 1) [4a]. The *iso*-propyl and cyclohexyl derivatives are too weak acids to protonate reagent **1** to a significant extent, therefore achieving only a low degree of activation and thus leading to a small relative rate. The other acids, however, are deprotonated to a sufficiently large degree such that destabilizing or stabilizing effects of the negative charge on the oxygen atom become pronounced in a linear fashion, i.e. a consistent negative charge is obtained during the rate-determining step. Furthermore, there seems to be no competition between activation of reagent **1** and nucleophilicity of the resulting anion—a situation which would lead to "downward" bending for electronegative substituents ($\sigma^*_{corr} > 0$) as the nucleophilic attack on the iodonium core would become the rate-determining step (Scheme 2, step 2).

Deprotonation of the hydrogen phosphate at the stage of the initial equilibrium (Scheme 2, step 1) is bound to change the electronic environment of the central phosphorus atom. With a reported $\sigma_{inductive}$ value of 0.29 for the hydroxy substituent and a $\sigma_{inductive}$ of −0.16 for the oxide anion, one expects the oxygen of interest (Scheme 2, highlighted) to change from a very electronegative situation to a less electron-withdrawing one [10]. According to the Walsh–Bent rule, this will lead to an increased *s*-character of the phosphorus oxide anion bond and hence result in a pyramidalization-type deformation of the molecule itself [11]. Therefore, the angles between the alkoxide substituents and the oxide anion are expected to increase and thus decrease the steric strain imposed by the increased radius of the oxide anion. Although this simplistic rationalization neglects structural changes due to resonance effects it may still account for the observed reactivity. The *iso*-propyl, cyclohexyl and neopentyl substituent have similar inductive properties with calculated σ^*_{corr} values of −0.09, −0.08 and −0.07, respectively, and would thus be expected to have similar relative rates. However, neopentyl is found to react significantly faster (Table 1). The proposed release of steric strain energy (*vide supra*) is expected to be larger for neopentyl ($E_{S,corr} = -1.44$) than for *iso*-propyl and cyclohexyl ($E_{S,corr} = -0.40$ and -0.50, respectively) and is thus compensating to a greater extent for lessened acidity due to inductive effects.

Analysis of the ^{19}F and ^{31}P NMR towards the end of the reaction of dimethyl hydrogen phosphate shows formation of substantial amounts of dimethyl fluorophosphate.[7] These are proposed to initially stem from thermal decomposition of the product formed to yield carbonyl fluoride. The latter reacts with water liberating CO_2 and two equiv of HF, which lead to further autocatalytic decomposition. Competition between formation and decomposition of product thus allows explaining the low yields observed and the fact that the reagent is apparently consumed faster than product is formed (Fig. 1) (Scheme 3).

3. Conclusions

The electrophilic trifluoromethylation of hydrogen phosphates was probed by means of relative rates determined through initial rate experiments carried out under pseudo first order conditions. Through a Taft analysis of the data obtained it could be shown that a negative charge is building up during the rate-determining step. As a ρ^* value <1 was obtained it could be concluded that the reaction is only mildly sensitive towards inductive effects. Furthermore, the observed acceleration due to increased steric bulk of the substrate's substituent is plausibly accounted for by a subtle electronic effect. However, strong competition between formation of the desired product and its autocatalytic decomposition to the corresponding dialkyl fluorophosphates undermines the utility of the reaction, so far. Further studies towards reaction optimization and isolation, based on the mechanistic investigation presented herein, are currently on-going and will be presented in due course.

4. Experimental

4.1. General procedure 1: synthesis of alkyl chlorophosphates

Anhydrous $CuCl_2$ (2.1 equiv.) was suspended in THF, then cooled to 0 °C. To the resulting green/brown suspension was added the corresponding alkyl phosphonate (1 equiv.) in THF in one portion under vigorous stirring. The cooling bath was removed and the mixture was allowed to warm to ambient temperature over 25 min. The mixture was then concentrated under reduced pressure and the residual light brown solid was extracted twice with 100 mL pentane and filtered over celite. Concentration of the clear pentane solution under reduced pressure followed by

[7] Spectral data δ_F (376.5 MHz, $CDCl_3$) −85.3 (d, $J = 978.4$ Hz), δ_P (162.0, $CDCl_3$) −5.9 (d, $J = 978.3$ Hz) are in accordance with resonances reported in: T. Sierakowski, J.J. Kiddle, Tetrahedron Lett. 46 (2005) 2215.

distillation at HV yielded pure alkyl chlorophosphates. All products were stored at −17 °C under an atmosphere of argon. All characterization data can be found in the electronic supplementary information.

4.2. General procedure 2: synthesis of dialkyl hydrogen phosphates

The corresponding alky chlorophosphate (1 equiv.) was dissolved in THF and the resulting colorless solution was cooled to 0 °C. Then, aqueous NaOH (1 M, 1 equiv.) was added dropwise. The resulting mixture was stirred vigorously at 0 °C for 30 min, then concentrated under reduced pressure. The residual wet white solid was extracted with Et_2O and the organic layer was dried over $MgSO_4$. After filtration, the resulting solution was concentrated under reduced pressure to yield the crude product as a viscous oil. The latter was dissolved in a saturated solution of $NaHCO_3$ that was subsequently washed three times with the same amount of CH_2Cl_2. The aqueous layer was then acidified with HCl (1 M) until the pH value was between 0 and 1 and extracted with CH_2Cl_2 (3× 50 mL). The combined organic layers were dried over $MgSO_4$, then concentrated under reduced pressure to yield pure dialkyl hydrogen phosphates. All products were stored at −17 °C under an atmosphere of argon. All characterization data can be found in the electronic supplementary information.

4.3. Measurement of initial rates

All reactions were monitored by ^{19}F NMR spectroscopy using a Bruker AVANCE DPX 400 MHz NMR spectrometer operating at 376 MHz. The sample temperature of 313 K (40 °C) was maintained using a Bruker BVT3000 temperature control unit calibrated with a digital thermometer fit to a 5 mm NMR tube. Initially, the shim was optimized for a sample containing only reagent **1** and the internal standard, α,α,α-trifluorotoluene. A spectrum (ns = 8, $d1$ = 10 s) of this blank was recorded in order to determine the initial $I_{reagent,blank}/I_{standard,blank}$ ratio through integration. Then, to a second tube containing a solution of the appropriate hydrogen phosphate (0.48 mmol, 10 equiv.) in 0.40 mL $CDCl_3$ was added 0.10 mL of a solution containing reagent **1** (0.48 mM, 1 equiv.) and α,α,α-trifluorotoluene (0.48 mM, 1 equiv.). The second tube was shaken vigorously for approx. 10 s, then inserted into the spectrometer and the acquisition was started.

A pseudo 2D acquisition program was used, averaging 4 subsequent spectrums recorded in intervals of 27 s to one data point. Thus, a data point was obtained every 2 min along the reaction coordinate. The data obtained was processed using the XWinNMR 3.5 software package. Further detail concerning data processing can be found in the electronic supplementary information.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jfluchem.2011.08.014.

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