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Size-dependent rate acceleration in the silylation of secondary alcohols: the bigger the faster†

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Relative rates for the reaction of secondary alcohols carrying large aromatic moieties with silyl chlorides carrying equally large substituents have been determined in organic solvents. Introducing thoroughly matching pairs of big dispersion energy donor (DED) groups enhanced rate constants up to four times, notably depending on the hydrogen bond donor ability of the solvent. A linear correlation between computed dispersion energy contributions to the stability of the silyl ether products and experimental relative rate constants was found. These results indicate a cooperation between solvophobic effects and DED-groups in the kinetic control of silylation reactions.

Introduction

Aromatic interactions¹ play a central role in diverse fields such as organic synthesis,² supramolecular self-assembly,^{3–5} molecular recognition⁶ or protein and peptide structures.⁷ They mainly result from the sum of three terms:^{8,9} (1) an electrostatic component due to the electronic nature of the substituents at the interacting surfaces,¹⁰ (2) London dispersion interaction^{11–14} as the attractive component of van der Waals forces, which arise due to interactions between induced dipoles,¹⁵ and (3) the solvophobic or hydrophobic effect, which results from a balance between solvent–solvent and solvent–solute interactions.^{16–18} Whereas numerous studies have detailed the nature of the electrostatic component,^{19–24} it is still a challenge to quantify individual dispersive and solvophobic effects in solution.²⁵ Recent studies by Cockroft *et al.*^{26–29} and Shimizu *et al.*^{30,31} employ torsional molecular balances³² to measure these effects through the quantification of conformational equilibria. Most of the studies conclude that the dispersive interactions are of minor importance in solution³³ and that the major contribution to the stabilization of the folded state results from the balance of solvent–solvent and solute–solvent interactions. The conceptually similar idea of using sizeable (rigid) dispersion energy donor groups (DED-group) in reagents and/or ligands in the development of stereoselective catalytic processes has also been explored recently,^{2,34} where it has been found that the appropriate placement of interacting DED-moieties in a system can lead to higher selectivity. Interactions between DED groups in bimolecular (associative) reactions were recently analysed for

acylation reactions of alcohols.^{34,36} For this latter class of reactions we have found that acylations mediated by TCAP (9-azajulolidine, marked in red in Fig. 1a) are fastest for pyrenyl-substituted secondary alcohols (marked in green Fig. 1) as compared to alcohols carrying smaller aromatic or even aliphatic substituents.³⁵ In contrast, reaction rates hardly vary for acylation reagents of different size, which can most easily be accommodated in the general transition state structure shown in Fig. 1a. In the following we explore the question whether the silylation of secondary alcohols with silyl chloride reagents can be accelerated in a similarly targeted fashion through the use of sufficiently large DED substituents in the reagents and substrates. The silylation of alcohols is of outstanding importance in protection group strategies for the synthesis of complex molecular targets,^{37,38} and any extension of the currently available toolset will obviously be helpful for organic synthesis in general. The base-catalysed silylation of alcohols is commonly assumed to follow a Lewis base- rather than a general base-catalysed mechanism.^{39–42} In contrast to acylation reactions,

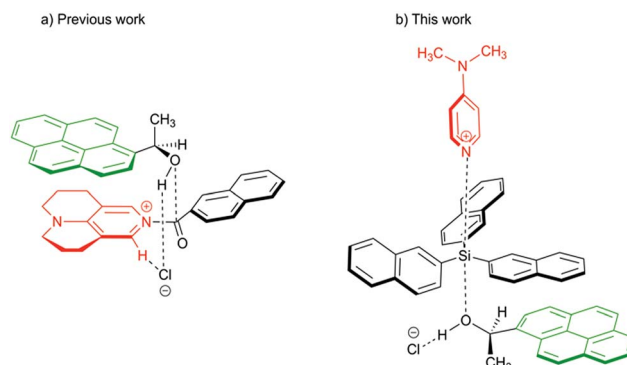


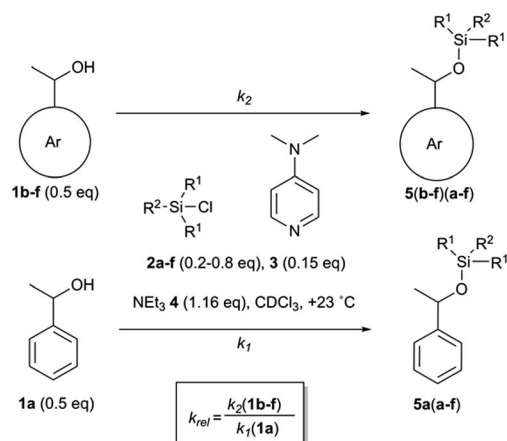
Fig. 1 Proposed transition structures for catalysed acylation (left) and silylation reaction (right) of 1-(1-pyrenyl)ethanol.

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silyl group transfer reactions proceed along an S_N2 -like pathway, which implies the relative orientation of catalyst, reagent and substrate shown in the transition state cartoon in Fig. 1b. For this type of transition state structure, stabilizing interactions between appropriately placed DED substituents are expected between the alcohol and the reagent, but not between

the alcohol and the catalyst. In order to probe this hypothesis, we have studied the reaction rates for the reaction of secondary alcohols with silyl chloride reagents carrying alkyl and aryl substituents of varying size. In addition, the influence of reaction temperature and solvent on the reaction rate was studied. The thermochemical stability of the products was explored by theoretical methods in an effort to quantify the dispersion energy contribution to the overall reaction driving force.



Scheme 1 Competition experiments between alcohol **1a** and **1b-f** with silyl reagents **2a-f**.

Results and discussion

Relative rate constants k_{rel} for the Lewis base-catalysed silylation of alcohols **1a-f** with silyl chlorides **2a-f** were determined in 1 : 1 competition experiments employing 1-phenylethanol (**1a**) as the reference system (Scheme 1 and Fig. 2). The other substrate alcohols derived from **1a** through annulation of one (as in **1b** and **1c**), two (as in **1d** and **1e**) or three (as in **1f**) benzene rings to its phenyl group. Depending on the particular position of annulation, this generates no additional repulsive 1,5-interaction with the alcohol oxygen atom (as in **1c** and **1e**), one additional 1,5-interaction (as in **1b** and **1f**), or two such interactions in **1d**. The *peri* positions responsible for the repulsive 1,5-interactions are marked by grey circles in Fig. 2. The silyl chloride reagents chosen here grow in size from trimethylsilyl

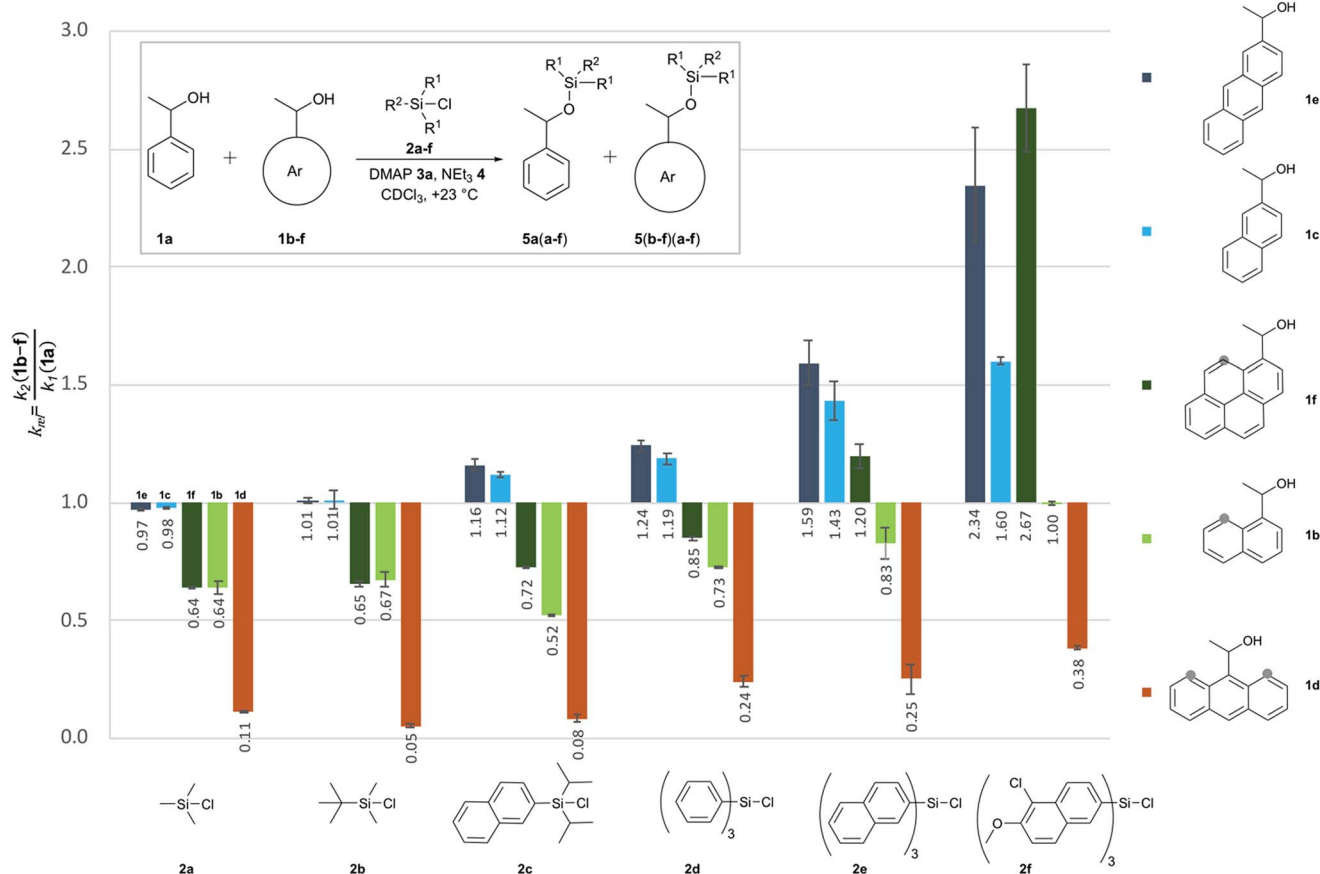


Fig. 2 Relative rate constants (k_{rel}) for competition experiments between reference alcohol **1a** and selected secondary alcohols **1b-1f** with silyl chlorides **2a-f**.

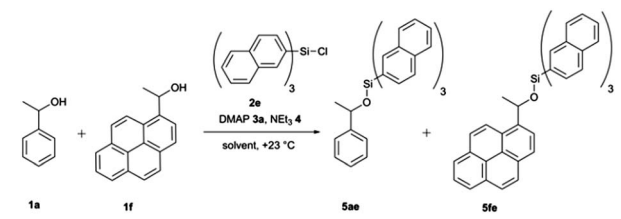


chloride **2a** to substituted trinaphthylsilyl chloride **2f** (see Fig. 2 and S1 of the ESI†). The competition experiments described in Scheme 1 involve equal amounts of reference alcohol **1a** and of one of the substrate alcohols **1b–f**, a quantity of one of the silyl chlorides **2** sufficient enough to obtain between 20–80% turnover of the substrate alcohols **1**, a catalytic amount (0.15 eq. relative to alcohols **1**) of *N,N*-dimethylaminopyridine (**3**, DMAP), and triethylamine (**4**) as the auxiliary base, in deuterated chloroform at a constant temperature of +23 °C. The relative rate constant k_{rel} defined as the ratio of effective rate constants k_2 (**1b–f**) over k_1 (**1a**) was used as main control parameter and obtained from the mole distribution of reactants and products after completion of the reaction as determined by ¹H NMR spectroscopy (for full details see ESI†). The resulting rate constant values are shown in Fig. 2 and in Tables S1–S5 of the ESI.†

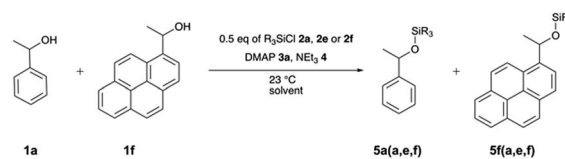
Relative reaction rates for the small trimethylsilyl chloride **2a** (TMSCl) reagent show no response to the size of the alcohol π -systems, but are sensitive to the number of repulsive 1,5-interactions. Reaction rates are therefore quite similar for alcohols **1a**, **1c** and **1e**, then drop notably for alcohols with one 1,5-interaction (**1b** and **1f**), and drop more strongly for the most hindered alcohol **1d**, which reacts nine times slower than **1a**. Moving to *tert*-butyldimethylsilyl chloride **2b** (TBDMSCl) as a sterically more hindered and overall larger reagent we find practically no change in relative rate constants k_{rel} , except for the most hindered alcohol **1d**, whose reactivity drops by another factor of two. With the results for smaller silyl chloride reagents in hand, we next investigated symmetrical silyl reagents **2d–2f** containing sizeable aromatic substituents.

Reactions with triphenylsilyl chloride (**2d**, TPSCl) differ from those with TMSCl in two key aspects. First, all k_{rel} values for silyl chloride **2d** are larger than those for TMSCl (**2a**), the sterically unhindered alcohols **1c** and **1e** now reacting even faster than the reference alcohol **1a**. Second, silyl chloride **2d** differentiates more strongly between alcohols of different size, but identical degree of steric hindrance. Reaction rates for alcohols **1b** and **1f**, for example, are quite similar for TMSCl (**2a**) and also for TBSCl (**2b**), but differ systematically for triphenylsilyl chloride (**2d**) in that the larger alcohol **1f** ($k_{\text{rel}} = 0.85$) reacts faster than alcohol **1b** ($k_{\text{rel}} = 0.73$). Both factors can be seen at work in an enhanced way in reactions of the even larger trinaphthylsilyl chloride **2e**, where the sterically hindered, but pyrenyl-substituted alcohol **1f** now reacts faster than the unhindered reference alcohol **1a** ($k_{\text{rel}} = 1.20$). Polar substituents were then added to the 5,6-positions of the naphthyl groups in silyl chloride **2e** in order to increase its overall polarizability and the contact surface with alcohol reagents. Relative reaction rates for the resulting silyl chloride **2f** (TN*SCl) are all significantly larger than those for trinaphthylsilyl chloride **2e** and appear to be mainly dominated by the size of the alcohol π -system. This makes pyrenyl-substituted alcohol **1f** the most reactive substrate, closely followed by the less hindered anthracenyl-substituted alcohol **1e**. A final test was performed with diisopropynaphthylsilyl chloride **2c** (DINSCl), which combines a single naphthyl with two α -branched isopropyl substituents. The results obtained for this reagent are basically those for trinaphthylsilyl chloride **2e**, but

Table 1 Relative rate constants (k_{rel}) for competition experiments between alcohol **1a** and **1f** with silyl chloride **2e** in different solvents



Entry	Solvent	k_{rel}
1	Tetrahydrofuran	0.59
2	Carbon disulfide	0.61
3	Dimethylsulfoxide	0.68
4	Dimethoxyethane	0.72
5	Hexafluorobenzene/chloroform-d ^a	0.74
6	Trifluorotoluene	0.79
7	Tetrachloromethane	0.84
8	Acetone	1.16
9	Chloroform-d	1.20
10	<i>t</i> -Amyl alcohol/chloroform-d ^a	1.21
11	Acetonitrile/dichloromethane ^a	1.36
12	Dichloromethane	1.38



^a Mixture 1 : 1 (v/v).

scaled down towards the results obtained for the trialkylsilyl chlorides **2a** and **2b** (Fig. 2). The spatial disposition of the substituents in the crystal structure of product **5fc** shows no direct interaction between the naphthyl and pyrenyl surfaces (see ESI†). Assuming a similar structure in the transition state, relative rates seem to be influenced by the isopropyl as well as the naphthyl substituents. The results presented in Fig. 2 can also be analysed from the point of view of each reacting alcohol (see Fig. S2†). While the 9-anthracenyl alcohol **1d** containing two *peri* hydrogen atoms is for all silyl chlorides much slower than **1a**, the sterically not hindered alcohols **1c** and **1e** react with all silyl reagents **2** equally fast or faster than **1a**. In the 1-pyrenyl- and 1-naphthyl-substituted alcohols (**1f** and **1b**) the relative rate constants are determined by a balance between interactions of the two aromatic surfaces and repulsive steric effects, the former one being dominant in the case of TN*SCl **2f**. In all of the pairs k_{rel} increases with the growth of the DED-substituent at the silicon centre, which confirms that the size of interacting aromatic surfaces located at the alcohol and silyl substrates determine the chemoselectivity of the silylation reaction.

With the purpose of quantifying the influence of the reaction medium on the relative rate constants, the competition experiment between the reference alcohol **1a** and the biggest alcohol **1f** with TN*SCl **2e** was carried out in different solvents. This choice was motivated by two main considerations: (1) both



alcohol **1f** and TNSCl **2e** carry the biggest non-substituted DED-substituents and (2) using alcohol **1f** the balance between attractive aromatic interactions and repulsive steric effects can be studied in different solvents. The k_{rel} values measured in different solvents span a range from 0.59 in tetrahydrofuran to 1.38 in dichloromethane (Table 1, for details see ESI†). Strikingly, relative rates for the reaction of alcohol **1f** with the naphthyl-substituted silyl chloride **2e** were found to be in several solvents (entries 1–3) very similar to k_{rel} of the reaction of this alcohol **1f** in the reference solvent CDCl_3 with TMSCl **2a** in which no aromatic interactions between alcohol and silyl moiety occur. Therefore, those solvents seem to cancel aromatic interactions almost completely and repulsive steric effects solely govern the relative rates. In contrast, k_{rel} for the silylation of alcohol **1f** increases up to 2.3 times in other solvents like acetone, chloroform and dichloromethane. In order to prove that those solvent effects are causally related to aromatic interactions, reactions between alcohols **1a** and **1f** with silyl reagents of various sizes were explored by competition experiments in CDCl_3 as the reference solvent, and in tetrahydrofuran and dichloromethane as the solvents with the smallest and largest k_{rel} values in Table 1 (Fig. 3). For TMSCl (**2a**) as the smallest reagent, only a negligible solvent sensitivity of k_{rel} was found (Fig. 3), while for the largest reagent TN*SCl **2f** an increase in solvent sensitivity as compared to the relatively smaller TNSCl **2e** is observed. Hence, the observed solvent effects are due to the significant impact of solvents on size-dependent effects, which was also reported in other studies.^{26,27,43–46} Distinguishing the different contributions of polarizability (π^* and δ), hydrogen-bond donor (α) and acceptor ability (β) via the linear solvation energy relationship developed by Kamlet and Taft^{47,48} revealed that solvent effects are widely independent of the polarizability of the solvent, but correlate strongly with the hydrogen bond donor ability of the solvent (see eqn (S12) of ESI†). This can actually be further condensed to a direct correlation of the experimental k_{rel} values with the general α parameter proposed by Hunter (Fig. 4).¹⁷ Considering that the hydrogen-bond donor ability of aromatic C–H groups is commonly found to be in the range of $\alpha = 1.0$ – 1.4 the origin of solvent effects can be clarified. Thus, for solvents with $\alpha < 1$

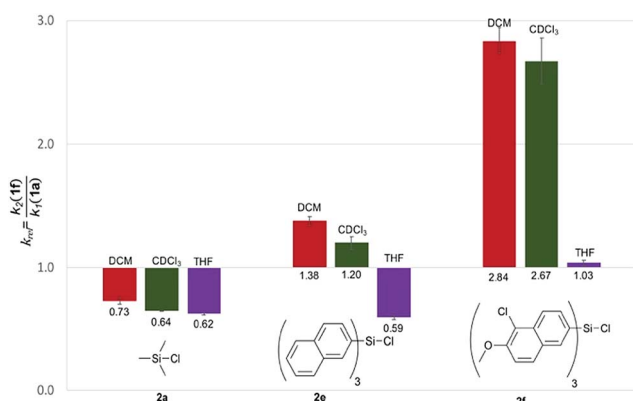


Fig. 3 Relative rate constants k_{rel} for the reaction of alcohols **1a** and **1f** with silyl chlorides **2a**, **2e** and **2f** in different solvents.

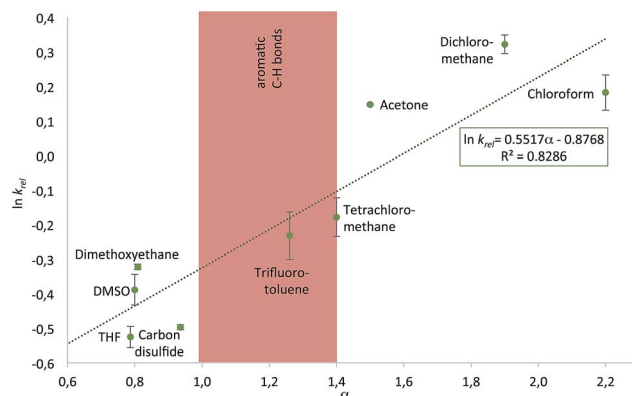


Fig. 4 Plot of experimental $\ln k_{\text{rel}}$ for the reaction of alcohols **1a** and **1f** with silyl chloride **2e** in different solvents against the solvent hydrogen bond donor parameter α defined by Hunter.¹⁷

such as THF and CS_2 hydrogen bonds of aromatic C–H-bonds with solvent molecules dominate the system whereas interactions of the aromatic surfaces of the alcohol and silyl moieties are minimized. Therefore, reaction rates are barely influenced by the different size of the aromatic systems of the two competing alcohols. As H-bonds between the aromatic C–H-bonds and the solvent get less relevant in solvents with $\alpha > 1$ such as chloroform and dichloromethane, desolvation of the alcohol and silyl substrates occurs and as a consequence solvent–solvent as well as aromatic solute–solute interactions become more dominant.¹⁷ Both the solvophobic effect of solvent molecules forming additional hydrogen bonds among each other and the attractive dispersion forces between the DED-groups can then enhance the rate of the reaction dependent on the size of the aromatic surfaces.

Differentiating the contributions of the aforementioned two types of effects is one main focus of the ongoing debate on aromatic stacking. The $\ln k_{\text{rel}}$ determined in different solvents listed in Table 1 were therefore also analysed in terms of the solvent cohesive energy density (ced) as key parameter for the strength of the solvophobic effect of a solvent.²⁷ Whether a higher ced value leads to an increase or a decrease of relative rates appears to depend on the hydrogen bond donor ability of the solvent (Fig. S14 of ESI†): in solvents with a low α (e.g. THF) higher ced values lead to a reduction in relative rates, possibly through the reinforcement of unfavourable solvent–solute interactions. In contrast, for solvents with a higher H-bond donor ability (e.g. DCM) higher ced values lead to an increase in k_{rel} . Correlations are, however, not very strong in both cases and the ced is thus insufficient to explain the observed differences in k_{rel} . The influence of London dispersion interactions on the experiment shown in Table 1 was subsequently probed through selectivity measurements in CDCl_3 at different temperatures, as these interactions are known to be less temperature dependent than dipole-dominated interactions.¹¹ Measurements in the temperature range from -10 °C to $+23$ °C lead to similar k_{rel} values for the **1a/1f** substrate pair, but the accuracy of these measurements was not high enough for the reliable extraction of activation parameters (see ESI†).



In how far the relative reaction rates measured experimentally simply reflect the stability of the silyl ether products formed was explored by the calculation of reaction free energies in chloroform solution. Geometry optimizations were performed at the SMD(CHCl₃)/B3LYP-D3/6-311+G(2d)/6-31+G(d)^{49–53} level of theory, followed by single point energy calculations at DLPNO-CCSD(T)/def2-TZVPP^{54–56} level. Solvation free energies were obtained from single point calculations with the SMD(CHCl₃)/B3LYP-D3/6-311+G(2d)/6-31+G(d) model and added to the gas phase results in order to obtain the reaction free energies in solution $\Delta G_{298,\text{sol}}$ compiled in Fig. 5 (see ESI† for details). Focusing on the results obtained for pyrenyl-substituted alcohol **1f**, we find small and positive reaction energies for the smaller silyl chloride reagents. The positive sign for the reaction energy seen here derives from the fact that the calculated energies exclude the acid/base reaction between HCl and the auxiliary base NEt₃. This is in full agreement with experimental results showing basically no turnover between TBDMSCl (**2b**) and secondary alcohols in the absence of the auxiliary base.^{39,40} Reaction energies become more favourable and eventually also negative on increasing the size of the silyl chloride reagent. Interestingly, the *tert*-butyldimethylsilyl ether **5fb** is less stable than the trimethylsilyl ether **5fa**, most likely due to repulsive steric interactions between the *tert*-butyl and the pyrenyl substituents. Although the two interacting aromatic surfaces are the same in the products **5fc** and **5fe**, the last one is 18.2 kJ mol⁻¹ more stable than **5fc**. This energetic difference is possibly associated to the smaller polarizability of the isopropyl substituents than the naphthyl moiety at the Si atom in **5fc**. Regarding those results no significant correlations were found between the experimental k_{rel} and the differences between the $\Delta G_{298,\text{sol}}$ of the respective silyl ethers (see ESI†), which indicates

that the k_{rel} are purely kinetic phenomena. At this point, we were interested in computing the contribution of the dispersion component to the thermochemical stability of the products. Single point energy calculations were therefore performed at the B3LYP level lacking the D3 dispersion correction over the optimized structures at B3LYP-D3 level (third group, Fig. 5). It was found that $\Delta G_{298,\text{sol}}$ decreases dramatically (larger positive values) even indicating that these products would be thermodynamically unstable. The smallest dispersion contributions were found in the silyl ethers **5fa** and **5fb** with non-polarizable methyl and *tert*-butyl substituents. However, in the case of silyl ethers carrying bigger aromatic substituents at the Si centre, the dispersion component increases notably up to -85.7 kJ mol⁻¹ (**5ff**). Conformational analysis of silyl ether **5fe** as the silyl ether with the largest unsubstituted aromatic substituents reveals that aromatic surfaces for the best conformers are slightly twisted toward each other so that most non-covalent interactions⁵⁷ arise between the interacting π -surfaces with a small contribution of σ - π interactions (see Fig. 5 and ESI† for full details). Interestingly, linear correlations appear to exist between experimental k_{rel} values and differences in dispersion contributions between the respective substrate pairs $\Delta\Delta D_{298,\text{sol}}$, grouped by the number of 1,5-interactions at the alcohol substrate (Fig. 6). The similar slope reveals that sizeable DED-groups (higher $\Delta\Delta D_{298,\text{sol}}$) increases $\ln k_{\text{rel}}$ equally in both alcohol groups by 0.2 units per 10 kJ mol⁻¹ of additional dispersion contribution. That the data points for the unhindered alcohols **1c** and **1e** fall onto the same correlation line implies that it is irrelevant for the increase of k_{rel} whether the increase in $\Delta\Delta D_{298,\text{sol}}$ derives from growing the substrate alcohol or the silyl chloride reagent. The presence of one repulsive 1,5-interaction reduces the relative rate by 1.6 times

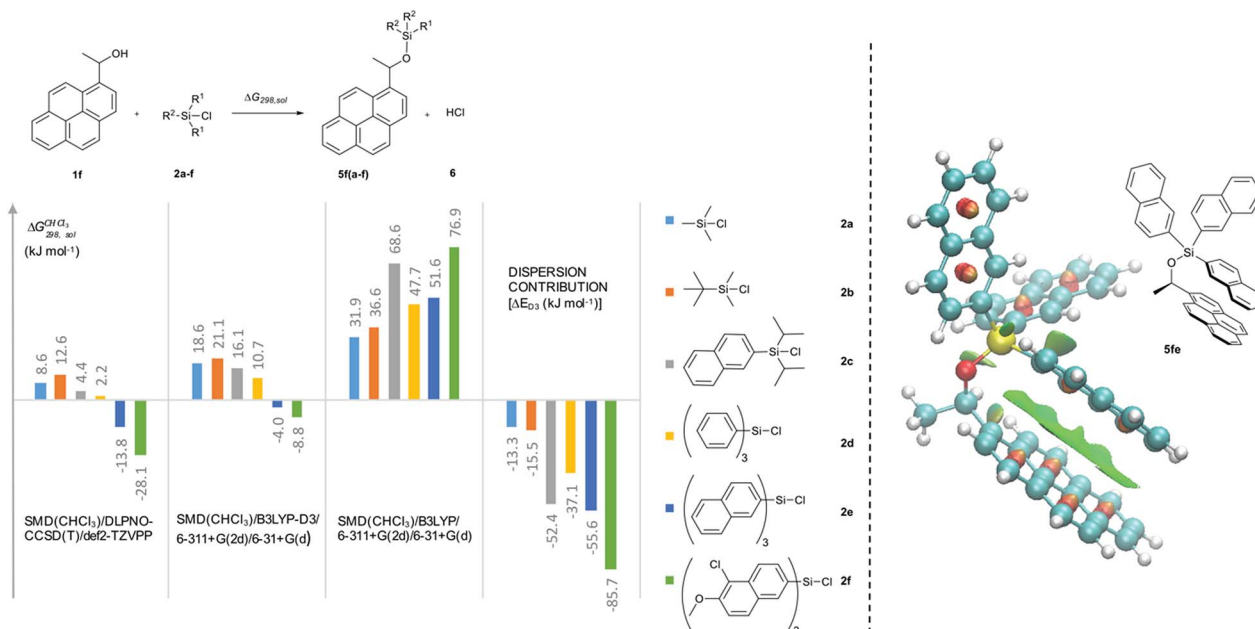


Fig. 5 Reaction free energies (kJ mol⁻¹) for the reaction of **1f** with the silyl reagent **2a–f** at different levels of theory. Computed non-covalent interaction surfaces (green) of the silyl ether **5fe**.



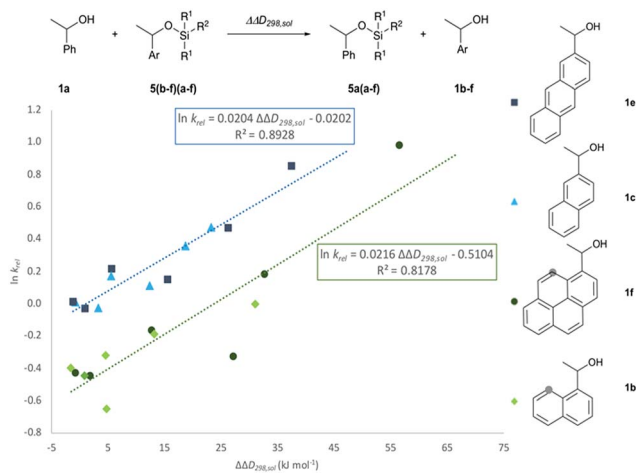


Fig. 6 Correlation of $\ln k_{\text{rel}}$ with calculated differences in the dispersion energy contributions, $\Delta\Delta D_{298,\text{sol}}$.

with respect to the non-hindered alcohols represented by the gap between the two correlation lines in Fig. 6. This analysis demonstrates that the experimentally measured relative rate constants k_{rel} directly relate to the size of the interacting surfaces and to repulsive steric effects in the alcohol substrates, whereby the dispersion energy component increases together with substrate size.

Conclusions

In summary, we have experimentally determined relative rates between two secondary alcohols bearing sizeable aromatic surfaces in silylation experiments designed as 1 : 1 competition experiments. In experiments with the comparatively small silyl chloride reagents TMSCl and TBDMSCl the relative rate constants are exclusively governed by repulsive steric effects provoked by the *peri* hydrogen atoms of the alcohol substrates. However, k_{rel} increases with the size of the DED groups at the silyl reagent, and aromatic interactions eventually dominate the silylation reactions with reagents as large as TN*SCl. No significant impact of the reaction temperature on k_{rel} has been found. In contrast, k_{rel} depends notably on the solvent used in the competition experiments. While size effects of the interacting aromatic surfaces appear to be cancelled in solvents with poor hydrogen bond donor abilities like tetrahydrofuran, they magnify as solvent–solute interactions get less important in halogenated solvents such as chloroform or dichloromethane depending to a notable extent on the higher solvophobic effect. Computed reaction free energies for the formation of silyl ether products predict that the dispersion component plays a key role in their thermochemical stability. Furthermore, linear correlations were found between experimental k_{rel} values and the dispersion contribution to the silyl ether formation energy. Therefore, the interplay of attractive dispersion forces and the solvophobic effect enhances relative rates for the silylation of a secondary alcohol up to 4.5 times. In this sense, the combination of sterically less hindered alcohols, tailor-made silyl

chloride reagents with bigger DED groups and thoroughly chosen solvents could enhance rate constants even further than in the systems presented here.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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