Tetrahedron Letters 56 (2015) 642–645

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Stereoelectronics of silyloxybenzoic acids

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ARTICLE INFO

Article history:
Received 13 November 2014
Revised 1 December 2014
Accepted 5 December 2014
Available online 12 December 2014

Keywords:
Stereoelectronic effects
Hydrogen bonding catalysis
Umpolung

ABSTRACT

Synthetic organic chemists generally think of silyl ethers as easier-to-cleave alkyl ethers, frequently neglecting to consider both the unique facets of elemental silicon and the size of commonly used trialkylsilyl protecting groups. In this study, several *ortho*- and *para*-silyloxybenzoic acids were investigated spectroscopically and as catalysts for a Friedel–Crafts reaction, with results highlighting some of the underestimated aspects of trialkylsilyloxyl substituents.

Introduction

Since their diversification and popularization by Corey in the 1970s,[1,2] trialkylsilyl protecting groups have seen extensive use in organic synthesis for the masking of hydroxyl substituents.[3] Silyl ethers can be easily accessed from the parent alcohol under mild conditions and are readily hydrolyzed using aqueous fluoride solutions. The orthogonality of these conditions to those affecting other functionalities has made silyl ethers among the most popular choices for hydroxyl group protection.

There is much similarity between trialkylsilyloxyl and alkoxyl substituents including their relative inertness. Interestingly, due to their wide use as protecting groups trialkylsilyloxyl substituents are more prevalent in modern chemical literature than similarly branched alkyl substituents. These two facts can lead researchers to (1) neglect to consider both the unique structural and functional characteristics of silicon and (2) underestimate the sheer size of trialkylsilyloxyl groups when discussing and using molecules containing such functionality.

With regard to the first statement—silicon's uniqueness—there are two salient points to make. First, silicon's size renders both the Si–O bond longer than a C–O bond in analogous dialkyl ethers and the ethereal bond angles more obtuse in the silyl derivatives.[4] In this sense, silyloxyl groups can have less of a steric impact than their carbonaceous analogs; such an effect can be seen in the axial/equatorial distribution of silyloxycyclohexanes.[5] Second, silicon possesses *d* orbitals and thus the possibility to form hypervalent structures.[6–9]

The second statement—the relatively large size of trialkylsilyloxyl groups when compared to commonly seen alkoxyl groups[10]—in certain contexts can overwhelm any perceived steric relief offered by the aforementioned longer bond lengths and wider bond angles of silyl ethers. For example, trimethylsilylated prolinol relies on the bulk of the silyl substituent to direct the stereochemistry in reactions catalyzed by such reagents.[11–13]

Aromatic systems offer a useful scaffold upon which to study the stereoelectronics of substituents through established Hammett principles.[14] While oxygen-linked substituents are electronically favored to lie coplanar to the aromatic ring, more sterically demanding environments may destabilize conformations, precluding electron donation of the oxygen lone pair into the aromatic π system (Fig. 1);[15,16] analogous conformations have also been observed in the crystal structure of a silyl enol ether.[17] Alabugin and co-workers have recently demonstrated the chameleonic electronic nature of the methoxyl substituent on a specific aromatic system: while traditionally thought of as an electron donating substituent, in the perpendicular conformation the substituent can be electron withdrawing.[18]

A recent publication from the labs of Lloyd-Jones and Booker-Milburn demonstrated a similar umpolung principle in a different conjugated system: the amide.[19] In this work, methanolysis of bulky amides was examined and a general correlation between this rate and the size of the N-substituents was established. This phenomenon is explained by a destabilization of the conformation that allows for overlap between the nitrogen lone pair and the π bond of the carbonyl, turning the nitrogen substituent into an inductively electron withdrawing group.

Experimental investigation of *para*-silyloxybenzoic acids

To this point the stereoelectronic effects of trialkylsilyloxyl groups on aromatic rings have not yet been systematically

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http://dx.doi.org/10.1016/j.tetlet.2014.12.013
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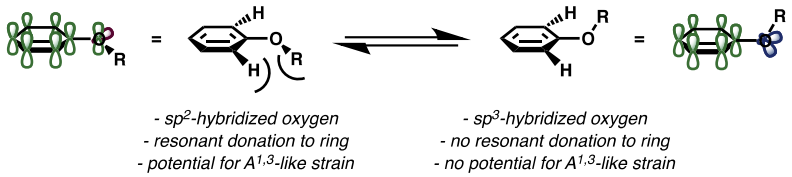


Figure 1. Steric congestion between the R group and adjacent aryl proton can result in a destabilization of the preferred coplanar conformation altering the electronics of the ring. Relevant stereoelectronic effects for each conformation are listed beneath simply.

experimentally examined.[20] Hammett substituent constants (σ) have been published for the trimethylsilyloxyl substituent and these are nearly identical to those of the methoxyl group,[14] however these values are derived from the ionization of substituted benzoic acids in an aqueous solution—conditions under which a silylated phenol will be hydrolyzed.

Given the insolubility of larger trialkylsilyloxybenzoic acids in water and the deleterious hydrolysis reaction, an alternative model system must be applied to evaluate such substituents: in this work, the benzoic acid-catalyzed Friedel–Crafts alkylation of indole with β-nitrostyrene through hydrogen bonding was used (Fig. 2). This reaction has previously been demonstrated to be sensitive to small electronic alterations of the acid.[21] An electron-poor arene results in a better hydrogen bond donor, biasing the reversible association of the β-nitrostyrene to the benzoic acid catalyst in favor of the reactive electrophile. Conversely, an electron-rich arene makes for a worse hydrogen bond donor, discouraging formation of the active electrophilic species. This platform was found to be suitable for examination of the stereoelectronic effects of silyloxyl substituents on benzoic acids.

The synthesis of silyloxybenzoic acids was achieved in a two-step process. Benzyl hydroxybenzoates (**1**, **2**) were silylated and subsequently hydrogenolyzed to yield *para*- (**3**) and *ortho*-silyloxybenzoic acids (**4**) (Fig. 3).

The baseline rate for the Friedel–Crafts reaction was established by using benzoic acid as the hydrogen bonding catalyst, which resulted in a yield of 25% (Table 1, entry 1). When silyloxyl substituents were present at the *para* position (**3**), the yield of the reaction increased significantly (Table 1, entries 2–4). A similar effect was observed for the *para-tert*-butoxybenzoic acid derivative (Table 1, Entry 6). Notably, Hammett values for each of these investigated substituents have not been previously published. This increased catalytic activity suggests the substituent is helping to stabilize

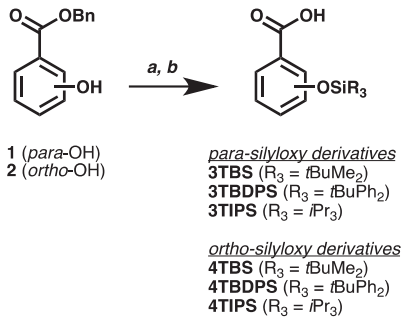


Figure 3. Synthesis of silyloxybenzoic acids **3** and **4**.

the increased electron density on the carboxyl group when acting as a hydrogen bond donor. This effect is not exacerbated by increasing size of the alkyl groups on the silicon.

Disappointingly, *para*-anisic acid (Table 1, entry 5), *para*-ethoxybenzoic acid, and smaller silyl ether derivatives (TMS, TES) were not soluble under the conditions of the reaction. Information regarding the effect of placing a methoxyl group *para* to the carboxyl in this system can be inferred from the work of Mattson and coworkers, who observed in two separate systems a decrease in the efficiency of their hydrogen bond catalysts when such a structural modification was introduced.[21] Such activity is consistent with the widely accepted designation of the methoxyl substituent as an electron donating group.

Additional support for the steric-induced electronic effect of the bulky silyloxyl substituents may be seen in the IR stretch of the carbonyl. Benzyl benzoates bearing the *para*-silyloxyl substituents (**9**) displayed a stretching wavenumber higher (Table 1, entries

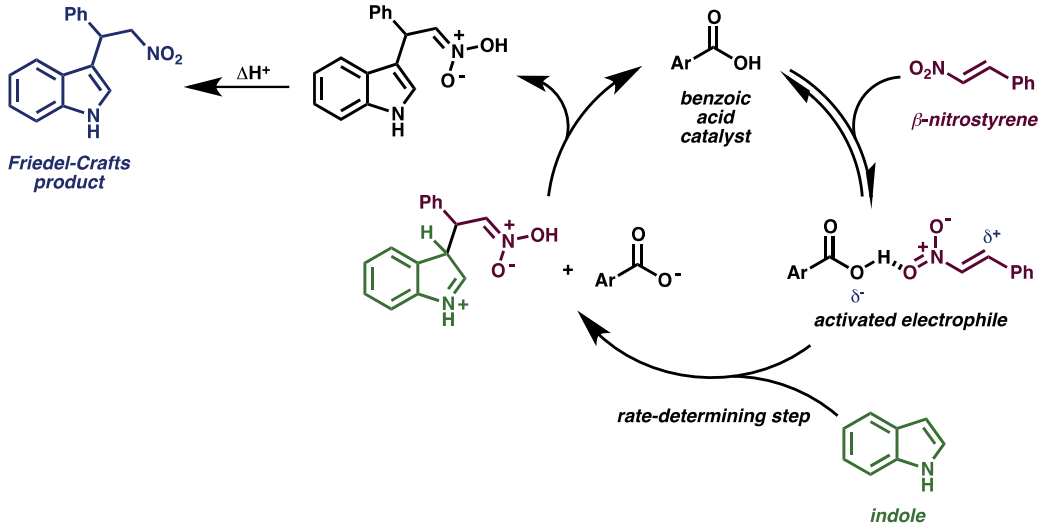
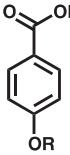
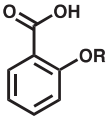
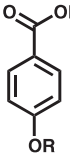
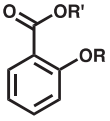
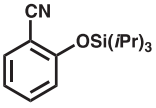


Figure 2. Reaction platform (and a proposed catalytic cycle) used to study the stereoelectronic effects of silyloxyl substituents on benzoic acid hydrogen bonding.

Table 1
Catalytic yields and relevant spectroscopic data for all investigated benzoic acid derivatives

Entry	Compound	Structure	R	R′	Yield[a] (%)	^{29}Si (ppm)	Δ^{29}Si (p–o)[b]	Carbonyl IR stretch[c]	ΔIR (p–o)[b]
1	**5**	Benzoic acid	n/a	n/a	25	n/a	—	1677	—
2	**3TBS**		$SiMe_2tBu$	n/a	42	22.3	—	1673	—
3	**3TBDPS**		$SiPh_2tBu$	n/a	48	−4.4	—	1671	—
4	**3TIPS**		$Si(iPr)_3$	n/a	45	17.4	—	1682	—
5	**6**		Me	n/a	—	n/a	—	1675	—
6	**7**		*t*Bu	n/a	48	n/a	—	1678	
7	**4TBS**		$SiMe_2tBu$	n/a	19	28.2	−5.9	1657	16
8	**4TBDPS**		$SiPh_2tBu$	n/a	32	−0.5	−3.9	1676	−5
9	**4TIPS**		$Si(iPr)_3$	n/a	9	24.6	−7.2	1654	28
10	**8**		Me	n/a	17	n/a	—	1664	11
11	**9TBS**		$SiMe_2tBu$	Bn	6	22.3	—	1717	—
12	**9TBDPS**		$SiPh_2tBu$	Bn	6	−4.7	—	1714	—
13	**9TIPS**		$Si(iPr)_3$	Bn	4	17	—	1715	—
14	**10**		Me	Me	3	n/a	—	1708	—
15	**11**		Me	Bn	—	n/a	—	1709	—
16	**12TBS**		$SiMe_2tBu$	Bn	3	22.3	0	1729	−12
17	**12TBDPS**		$SiPh_2tBu$	Bn	—	−5.4	0.7	1729	−15
18	**12TIPS**		$Si(iPr)_3$	Bn	—	16.7	0.3	1730	−15
19	**13**		Me	Me	3	n/a	—	1726	−18
20	**14**		n/a	n/a	—	18.1	—	2225	—
21	**15**		n/a	n/a	—	19.8	−1.7	2228	−3
22[d]	n/a	–	n/a	n/a	3	n/a	—	n/a	—

[a] Friedel–Crafts reactions (Fig. 2) run at 0.2 M in DCM with 20 mol % catalyst. Isolated yields are reported.
[b] This change is derived by subtracting the value of the *ortho*-silyloxyl compound version from that of the *para* version; the difference is listed with the respective *ortho*-silyloxyl compound.
[c] Infrared spectra acquired from neat compounds.
[d] Reaction run in the absence of any catalyst.

11–13) than the methoxyl-substituted derivative (**10**, **11**; Table 1, entries 14–15), indicating a shorter bond distance. This is consistent with the silyloxyl groups donating less electron density than the methoxyl substituent. It is worth noting that the similarity in absolute value between *para*-anisic acid (**6**; Table 1, entry 5), *para*-*tert*-butoxybenzoic acid (**7**, Table 1 entry 6), and the *para*-silyloxybenzoic acid carbonyl wavenumbers is due to the formation of carboxylic acid dimers in solution,[22] which overwhelms substituent effects on the stretching of the bond.

Computational investigation of *para*-silyloxybenzoic acids

To probe the energetics of both perpendicular- and parallel-oriented alkoxy- and silyloxybenzoic acids, paired examples were computationally optimized and the potential energy surfaces between them examined (Fig. 4).[23] Distinct differences were observed related to the size of the ethereal substituent. Compound **6** preferred orienting the relatively small methoxyl substituent coplanar with the arene ring by 12 kJ mol^{-1} (MP2/6-311+G(d,p)). In contrast, *para*-trimethylsiloxybenzoic acid showed essentially identical stabilities for coplanar and perpendicular conformers (with a 1–3 kJ mol^{-1} barrier between the two, depending on model chemistry) while **3TIPS** and *tert*-butoxyl **7** displayed distinct preferences for the perpendicular conformation (13 and 8 kJ mol^{-1}, respectively, MP2/6-311+G(d,p)). Although

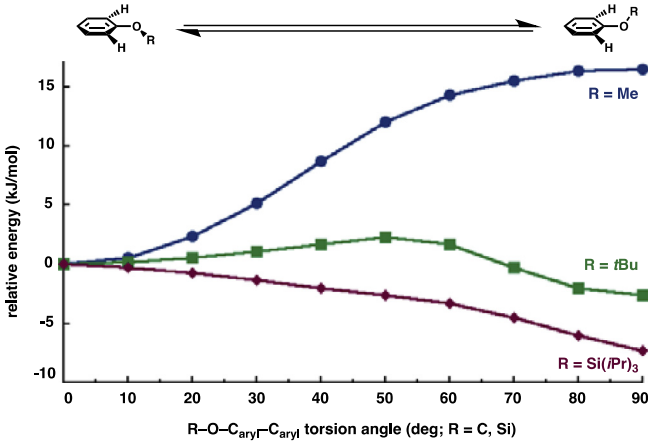


Figure 4. Potential energy surface scan data (wB97xd/6-31+G(d,p)) for rotation of the ethereal substituent from coplanar to perpendicular.

these energies do not connect directly to the yields shown in Table 1, they suggest that bulky ethereal substituents can adopt perpendicular conformations, rendering them electron withdrawing and subsequently increasing hydrogen-bonding catalyst activity.

Experimental investigation of *ortho*-silyloxybenzoic acids

In an effort to amplify the steric effects, a series of *ortho*-silyloxybenzoic acids were also evaluated as catalysts. It has been documented that *ortho*-alkoxybenzoic acids engage in intramolecular hydrogen bonding[24,25] and accordingly it is expected that such compounds should be worse intermolecular hydrogen bond donors and thus catalysts than the parent benzoic acid (**5**, 25%). While this is precisely what is observed for the methoxyl (**8**, 17%), TBS (**4TBS**, 19%), and TIPS (**4TIPS**, 9%) derivatives, the TBDPS variant (**4TBDPS**) in fact showed mildly enhanced (32%) catalytic activity (Table 1, entries 1 and 7–10).

The downfield shift of the ^{29}Si NMR signal when moving the silyloxyl substituent from the para to the ortho position provides evidence for intramolecular hydrogen bonding in solution causing a further polarization of the Si–O bond.[26] This effect is not seen in the benzyl ester precursors and is significantly less pronounced in the less sterically demanding silyloxybenzonitrile indicating this is not simply a result of the closer proximity of the electron-withdrawing carboxyl/cyano group.

Information regarding intramolecular hydrogen bonding can also be gathered from the IR data. Movement of ethereal substituents from *para* (**3**, **6**) to *ortho* (**4**, **8**) resulted generally in a wavenumber shift correspondent to a lengthening of the carbonyl bond, with the TBS and TIPS derivatives (Table 1, entries 7 and 9) having a more marked effect than the methoxyl group (Table 1, entry 10).

Interestingly, the IR spectra of the TBDPS variant suggest a shortening of the carbonyl bond when the substituent is moved from *para* to *ortho* (Table 1, entries 3 and 8). These data are consistent with the trend observed in both the benzoate ester series (Table 1, entries 16–19) and the examined benzonitrile (Table 1, entry 21) suggesting the dominant effect in this instance is simply the electronic effect of the movement of the substituent closer to the carbonyl. Such a finding indicates that the intramolecular hydrogen bond is not as prevalent in the *ortho*-OTBDPS derivative, suggesting the oxygen of the TBDPS ether is less effective as a hydrogen bond acceptor than the other investigated silyl ethers. TBDPS protecting groups are known to be more stable to acid hydrolysis than TBS or TIPS,[3,27] a phenomenon that may be explained in the same manner. Unsurprisingly then, compound **4TBDPS**, with a less intramolecularly hydrogen bonded proton, is more effective at catalyzing the examined Friedel–Crafts reaction (32%) than **4TBS**, **4TIPS**, and **8** (Table 1, entries 7–10).

Conclusions

This study provides insight into the conformation and activity of several silyloxybenzoic acids. The increased activity of the *para*-silyloxybenzoic acids may be explained by a destabilization of the conformation that allows for resonant contribution of the ethereal oxygen to the aromatic ring. The range of activities of the *ortho*-silyloxybenzoic acids may be explained by a combination of steric and electronic factors. Further studies on the stereoelectronic consequences of the conformation of silyloxybenzenes are ongoing.

Acknowledgments

The authors would like to thank Dr. Heike Hofstetter (University of Wisconsin, Madison) for spectroscopic training and assistance and Northern Illinois University, the Division of Research and Graduate Studies (Research & Artistry Opportunity Grant) and the Department of Chemistry & Biochemistry for funding. The NIU Computational Chemistry Laboratory (NIU CCL) is supported in part by the taxpayers of the State of Illinois.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.12.013.

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