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Stereoelectronics of silyloxybenzoic acids

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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 trialkylsilyloxy substituents.

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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 trialkylsilyloxy and alkoxy substituents including their relative inertness. Interestingly, due to their wide use as protecting groups trialkylsilyloxy 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 trialkylsilyloxy 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, silyloxy groups can have less of a steric impact than their carbonaceous analogs; such an effect can be seen in the axial/equatorial distribution of silyloxy cyclohexanes.⁵ Second, silicon possesses *d* orbitals and thus the possibility to form hypervalent structures.^{6–9}

The second statement—the relatively large size of trialkylsilyloxy groups when compared to commonly seen alkoxy

groups¹⁰—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 methoxy 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 trialkylsilyloxy groups on aromatic rings have not yet been systematically

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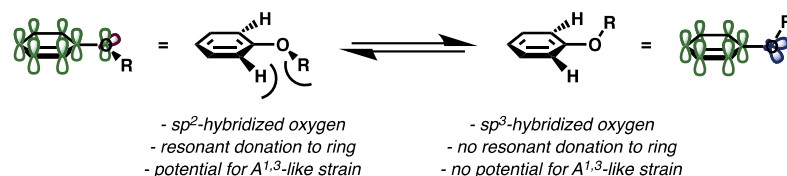


Figure 1. Steric congestion between the R group and adjacent aryl proton can result in a destabilization of the preferred coplanar conformation altering the electronics of the ring. Relevant stereoelectronic effects for each conformation are listed beneath simply.

experimentally examined.²⁰ Hammett substituent constants (σ) have been published for the trimethylsilyloxy substituent and these are nearly identical to those of the methoxy 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 silyloxy 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 silyloxy 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

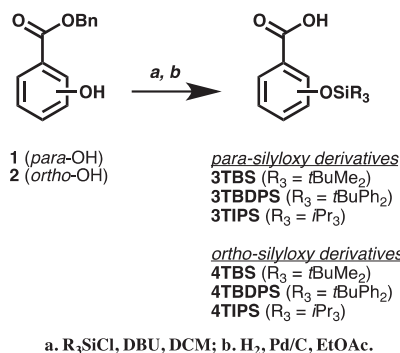


Figure 3. Synthesis of silyloxybenzoic acids **3** and **4**.

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 methoxy 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 methoxy substituent as an electron donating group.

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

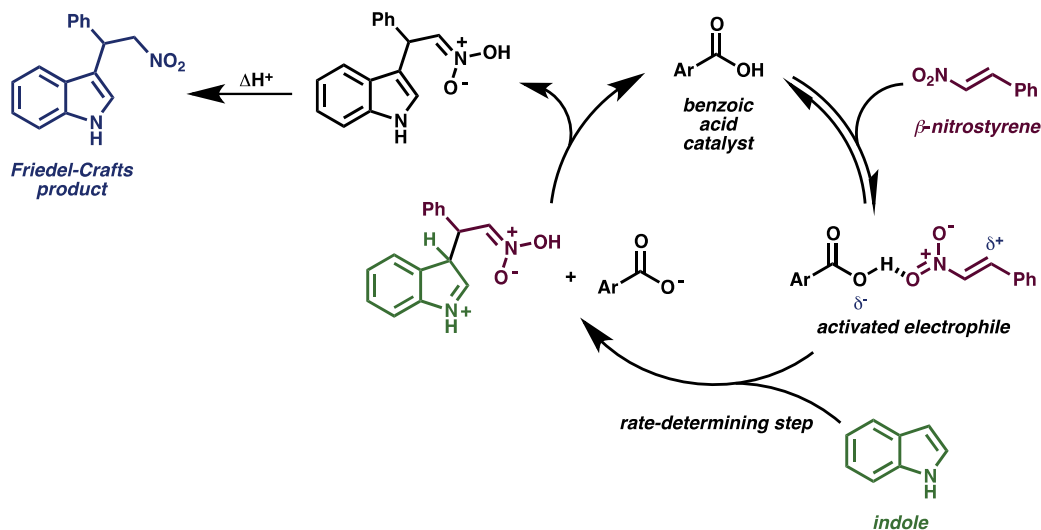


Figure 2. Reaction platform (and a proposed catalytic cycle) used to study the stereoelectronic effects of silyloxy substituents on benzoic acid hydrogen bonding.

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