The control of stereochemistry by the pentafluorosulfanyl group
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The influence of pentafluorosulfanylation on biological activity has been revealed in numerous comparative studies of biologically active compounds, but considerably less is known about the influence of pentafluorosulfanylation on reactivity. Among the distinctive properties of the pentafluorosulfanyl group is the profound dipole moment that results from introduction of this substituent. It has been shown that dipolar effects coupled with the steric demand of the SF₅ group may be employed to influence the stereochemistry of reactions, especially those processes with significant charge separation in the transition state. The Staudinger ketene-imine cycloaddition reaction is an ideal platform for investigation of dipolar control of diastereoselectivity by the pentafluorosulfanyl group.

Introduction

Numerous pentafluorosulfanyl(SF₅)-containing organic compounds¹⁻¹⁰ have been prepared that have potential utility in drug discovery, agrochemical synthesis and materials science. The surge of interest in this area is a consequence of the increasing availability of building blocks, or reagents, that were previously very difficult to access.⁷ Much of what is known about the effect of pentafluorosulfanylation is derived from comparative studies of biologically active trifluoromethylated compounds, where the trifluoromethyl (CF₃) group was replaced by an SF₅ group.¹¹⁻¹⁷ Reports of the physical chemical influences of pentafluorosulfanylation on aliphatic systems are especially fragmented and tentative.

Conformational control.

The SF₅ group has been variously described as a “super” CF₃ group¹⁸ or a tert-butyl isostere.¹⁹ The volume of the SF₅ group (55.4 Å³) is less than that of a tert-butyl group (76.9 Å³),¹⁻¹² but greater than that of a CF₃ group (34.6 Å³). The octahedral geometry around sulfur results in a dramatic reduction of the barrier to rotation of a carbon–SF₅ bond relative to carbon–carbon bonds. The longer carbon–sulfur and sulfur–fluorine bonds have other surprising conformational effects as a consequence of the octahedral geometry around sulfur. On incorporation into a hydrocarbon chain, the restricted rotation about the carbon–sulfur bond that results from interactions with nearby methylene groups, can lead to localized conformational rigidity of the alkyl chain.¹²⁻²²

Pentafluorosulfanyl substituents adjacent to hydroxyl groups also influence conformation. The constraint of the S–C–C–OH dihedral angle to ±85° by the SF₅ group²² cannot be rationalized by the stereoelectronic influences shown to constrain the dihedral C(CF₃)=C–C–OH angle in the analogous trifluoromethylated molecules. Stereoelectronic control of conformation by the SF₅ group involves very different orbital interactions, a consequence of the hypervalent sulfur of the SF₅ group.²²

Electronic effects.

The magnitude of the electron withdrawing effects of SF₅ (electronegativity, 3.65)²⁴ and CF₃ (electronegativity, 3.36)²⁴ are similar.²⁵⁻²⁶ When Hammett σᵣ values are compared, the value of SF₅ (0.68) is greater than that of CF₃ (0.54).²⁷ The greater σᵣ value of SF₅ (0.55) relative to the value for CF₃ (0.39) is indicative of a greater bond polarization, and is consistent with the electronic effects observed in the estimation of electronegativity.²⁵⁻²⁶ In contrast, σₓ values of 0.11 for SF₅ and 0.12 for CF₃²⁵⁻²⁶ indicate comparable resonance contributions from both functional groups to the respective σᵣ values.

Dipolar effects of the SF₅ group on reactivity.

The profound dipole of the hydrolytically and chemically stable⁷⁻³³ SF₅ group may be used to influence the stereoselectivity of reactions, especially those processes where there is significant charge separation in the transition state. The computationally determined dipole moment of pentafluorosulfanylmethane (2.78 D) (B3LYP/6-31G**) is significantly greater than that of 1,1,1-trifluoroethane (2.06 D) (B3LYP/6-31G**) and nearly as large as that of nitromethane (3.48 D) (B3LYP/6-31G**).

Steric demand, torsional strain, and electronic effects are well known to influence stereoselectivity.³⁴⁻³⁵ The staggered transition state of the Felkin-Anh model³⁶⁻³⁸ for carbonyl additions (Fig. 1, Structures A and B) can be supplanted by a modified Cornforth rationale (Fig. 1, Structures C and D)²⁰.
when a significant dipole is induced by a substituent.\textsuperscript{40-42} The Cornforth model is characterized by the antiperiplanar conformational preference of the dipole-inducing functional group (Fig. 1).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Predicted influence of SF\textsubscript{5} group on additions to an aldehyde according to the Felkin-Anh TS (top row; A, (l,k)-attack) favored; or the Cornforth TS (bottom row; C, (u,l)-attack) favored.}
\end{figure}

TS B and C both are consistent with formation of the ul product, with C having the most accessibility to the Re face of the aldehyde. The Cornforth model hence affords a rationale for the very diastereoselective addition of even non-sterically demanding nucleophiles to SF\textsubscript{5}-containing aldehydes as shown in Fig. 2.\textsuperscript{43}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{The diastereoselectivity of Grignard addition to an α-SF\textsubscript{5}-aldehyde is consistent with the Cornforth TS model. (ref. 45).}
\end{figure}

Enolate selectivity. Benzyl\textsuperscript{44, 45} methyl\textsuperscript{46} and octyl\textsuperscript{44} esters of pentafluorosulfanyl acetic acid have been employed in directed aldol condensations. The selective addition of boryl enolates of the benzyl and octyl esters to carbonyl groups formed anti-aldol products.\textsuperscript{44, 46} The specificity was the consequence of (\textit{Z})-enolate formation (n.b., the stereochemistry of the enolate a result of the pentafluorosulfanyl group being (\textit{Z}) to the higher priority of carbon of the benzylxoy group relative to boron of the enolate). Selective enolization apparently is a result of simple steric interactions.

Stereoselectivity in pericyclic reactions.

\textbf{[3,3]-Sigmatropic rearrangements.} The SF\textsubscript{5} group may control the stereochemistry of sigmatropic rearrangements by electronic or steric effects. Analogously, 7:1 ul to lk diastereoselectivity\textsuperscript{47} was found in a [3,3]-sigmatropic rearrangement of an allylic trifluoromethyl ester.\textsuperscript{48} In that stereoelectronically driven example, cyclization occurred opposite to the more electron-rich face of the double bond as would be predicted Cieplak analysis.\textsuperscript{49} Enol silyl ketene acetals prepared from the cinnamyl α-CF\textsubscript{3}- and α-SF\textsubscript{5}-acetates failed to demonstrate diastereoselectivity\textsuperscript{50} in the Ireland-Claisen rearrangement as a consequence of SF\textsubscript{5}-induced steric effects. However, [3,3]-sigmatropic rearrangement of SF\textsubscript{5}-acetates of aliphatic allylic esters proceed diastereoselectively due to the differential reactivity of the intermediate (E/Z) silyl ketene acetals.\textsuperscript{51} The potential diastereoselectivity of the rearrangement was degraded by the steric-induced accessibility of both chair- and boat-like transition states.

\textbf{[2+2]-Cycloaddition reactions.} The highly diastereoselective formation of SF\textsubscript{5}-containing β-lactams has been previously reported.\textsuperscript{52} A SF\textsubscript{5} group at a stereogenic center of the aldimine induced formation of the u,l-β-lactam \textit{rac}-1 very selectively by lk,lk-1,2 (Si,Si-S or Re,Re-R) cyclization, albeit in only modest yield (Fig.3).\textsuperscript{52} A more thorough investigation of the effect of pentafluorosulfanylation is necessary to assess the generality of dipolar stereocontrol by pentafluorosulfanylation. To that end a mechanistic study of the ketene-pentafluorosulfanylaldimine cycloaddition reaction was required.

\textbf{Results and discussion}

\textbf{The influence of the N-alkyl substituent on pentafluorosulfanyl aldimine reactivity.}

The pronounced electron withdrawing effect of pentafluorosulfanylation on the acidity of an adjacent proton may adversely affect pentafluorosulfanyl aldime formation. Even though the ketene-imine cycloaddition process is very well studied,\textsuperscript{53-62} systematic comparative studies of the influence of simple N-protection are far less abundant.\textsuperscript{62} Our hypothesis was that the 4-methoxybenzyl (PMB) group of pentafluorosulfanyl aldime \textit{rac}-4 (R\textsuperscript{1} = 4-MeOC\textsubscript{6}H\textsubscript{5} in Scheme 1) could render the imine nitrogen of \textit{rac}-4 more basic, stabilizing the intermediate iminium ion of A. However, the amine should not be so basic as to promote formation of enamine 5 or acyl enamine 8. Precedence for the formation of pentafluorosulfanyl enamine 5 can be found in comparison with the published reactivity of the trifluoromethylated aldime, N-ethyl 3,3,3-trifluoro-propanaldimine.\textsuperscript{53}
Consideration of the charge distribution (Fig. 5), geometry, and reactivity of azidoketene suggested that azidoketene may increase the rate of ring closure in the ketene-imine addition reaction relative to the rate of SF₅-facilitated acyl enamine formation. From computational studies at the MP4 level of theory, the C–C–N–N torsional angle of 120° of azidoketene, a consequence of the repulsive interactions of the N-lone pair with the adjacent π-system, may increase the propensity of the intermediate zwitterionic adduct I (Scheme 3) to rapidly cyclize.

**Scheme 1:** Staudinger reaction of benzylxketene and pentafluorosulfanyl aldimes. Trace amounts of enamine 8 were detected spectroscopically in the reaction mixture but were not quantitatively characterized.

Replacement of the para-methoxyphenyl (PMP) protecting group previously employed in the synthesis of rac-1 by the PMB group resulted in a modest reduction in the already limited β-lactam yield. Whereas introduction of an allyl moiety had a very modest effect on increasing the overall yield of rac-7 from the published values for PMP protected imines. By ³¹F NMR, there was no detectable reduction in the 3,4-diastereoselectivity (See Fig. 4) or the influence of the asymmetric SF₅-bearing carbon on diastereoselectivity during formation of reaction product rac-7 relative that previously observed with the PMP protected β-lactams.³²

**Scheme 2:** Staudinger reaction of azidoketene and pentafluorosulfanyl aldimes. Enamine 10 was not isolated and was only tentatively identified spectroscopically.

Due to the susceptibility of 4 to hydrolysis, the reactive imines were used in the cycloaddition reaction without purification. Unfortunately unreacted amine 3 or enamine 5 quickly consume the azidoketene or the acid chloride precursor in side reactions, reducing the formation of 9 and forming complex side products.

**Stereoochemistry of β-lactam formation**

Previously, the Staudinger reaction was shown to proceed through the E-imine. In this work, the lk ring closure product of conrotatory ring closure was confirmed for 6c by single crystal X-ray diffraction studies (See Electronic Supplementary Information, Fig S1). The lk ring closure that formed 9 was established by interpretation of the ¹H coupling constants utilizing the Haasnoot equation that employs electronegativity data in concert with spectroscopic results (See Electronic Supplementary Information, p S6-S11).

**Azidoketene in the Staudinger reaction**

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For 9a–c, the coupling constants $J_{ab} = 4.6$ Hz, $4.9$ Hz, and $4.8$ Hz, respectively, correspond to $H_2-C-C-H_3$ dihedral angles of $19–21^\circ$, angles that can only be consistent with $lk$ ring closures. These values were in addition consistent with those found for 7a and 7b, 4.9 Hz and 4.7 Hz respectively. In addition there was excellent agreement with the coupling constants determined in our previous work, 4.7–4.9 Hz.\textsuperscript{52} Validation of the stereocchemical assignment was possible in the case of 9a where $R = H$. From the $J_{bc}$ and $J_{ba,d}$ values, a model for 9 could be constructed that had an $S-C-C-N$ dihedral angle of $+165^\circ$, a dihedral angle consistent with that determined from SF$_5$-substituted $\beta$-lactam crystal structures.\textsuperscript{52}

Control of ring closure stereochemistry by the SF$_5$ group.

Diastereomeric excess. The reactive aldimines 4b or 4c would be predicted to react equally by the $lk,lk$ or $lk,ul$ reaction topicity,\textsuperscript{47} however the stereoergic SF$_5$-bearing carbon profoundly affected the ring closure.\textsuperscript{52} The descriptor 1,2-$lk,lk$ describes the ring closure step of the ketene-imine addition process (See I1 or I2, Scheme 3) where the $Re$-face of the ketene reacts with the $Re$-face of the imine and the stereoechemistry of pentafluorosulfanylated imine is $(R)$ as possible with 4b or 4c. Similarly when the imine 4 has the $(S)$ configuration and the $Si$-faces of the ketine and the imine react, the reaction topicity could be described as $1,2-lk,lk$. When the $Si$ face of the $(R)$-imine 4 reacts with the $Si$ face of ketene the reaction topicity can be described as $1,2-lk,ul$. As described below, the 3,4-stereochemistry of the $\beta$-lactam, products 7 and 9 reported in this work and the earlier described $\beta$-lactams\textsuperscript{52} requires $Re,Re$ or $Si, Si$ ring closure. The influence of the asymmetry of pentafluorosulfanylated carbon will be discussed subsequently.\textsuperscript{(Scheme 3)}

Required conrotatory ring closure for control of 3,4-stereochemistry. The zwitterionic intermediates I1 or I2 formed by reaction at the $Re$ and $Si$ faces, respectively, of azidoketene, can undergo conrotatory ring closure to form the $\beta$-lactam ring by either counterclockwise or clockwise rotation. The direction of rotation for closure is dependent upon the conformation of I1 or I2, and thus the geometry of approach to the ketene (Scheme 3). Diastereoselective $lk$ ring closure\textsuperscript{47} occurs on the bonding of the two reactive carbons (C3 and C4) of intermediate I by rotation through the smaller of the two possible dihedral dihedral angles.\textsuperscript{59}

In Fig. 6, the $^{19}$F NMR spectra of 9b prior to workup is consistent with the formation of a significant excess of a single diastereomeric $l,l$ pair\textsuperscript{47} in a very diastereofacially selective reaction. The principal pair of $^{19}$F resonances was favored by more than 20:1 over those of the minor $l,u$ diastereomers. The $l,l$ pair would correspond to the products shown in Fig. 6 when $R = Me$. The minor $l,u$ pair would be derived from the product where $Re$, $Re$-product is formed from (S)-4b and the $Si$, $Si$-product is formed from (R)-4b.

The role of the pentafluorosulfanylated stereogenic center on diastereoselectivity. Racemic 4b was found to form only a single racemic diastereomer 9b by $^{19}$F NMR. The addition of azidoketene to a single enantiomer, $\langle R\rangle$-4b in dichloromethane was modelled at the (SM8)M06-2X/6-31+G(d,p) level of theory (Fig. 7). Consistent with the recognized stepwise mechanism of the process,\textsuperscript{71-73} energies for the intermediate zwitterions I1 and I2 as well as those of the rate determining transition states TS1 and TS2 have been computed.

Irrespective of the endo or exo reaction\textsuperscript{71} of azidoketene (See Scheme 3) with $\langle R\rangle$-4b, the energy barrier to formation of transition states I1 or I2 was negligible, with less than a 1 kcal energy difference between the two states.\textsuperscript{74} The apparent absence of a barrier to reaction is consistent with reaction of a highly reactive ketene and an electron deficient imine. Torqueelectronic or torqueselective control\textsuperscript{75} of the diastereoselectivity of the ring closure process of the Staudinger reaction has been widely invoked\textsuperscript{72-74}.

The stable conformations computed for intermediates I1 and I2 (Scheme 3) are very similar to the transition state structures reported by Cossío.\textsuperscript{72} Torqueselectivity resulted from steric encumbrance by an inward turned methyl group (similar to the conformation found for I1) that disrupted stabilizing stereoelectronic interactions.
The stabilizing effects minimized repulsive filled-filled orbital interactions between a donor orbital and the σ orbital of the partially formed σ-bond that closes the β-lactam ring.\(^{72}\) In Cossío’s system the ~5 kcal lower energy transition state occurred when stabilizing interactions between the newly formed bond and the σ\(^*\) orbital of the C-O σ-bond were possible. In the ring closure of \(I_1\) or \(I_2\) such electronic effects are not likely to be as influential as carbon-sulfur NBO analysis confirms C-S bond interactions with adjacent σ bonds are significantly less effective than the C-O interactions of the Cossío example.\(^{76}\)

The concept of torquoselectivity can be extended to the reactions of 4b in the ketene-imine cycloaddition process, if the “inward” methyl group of \(I_1\) is recognized to destabilize the intermediate effectively reducing the barrier to ring closure. The antiperiplanar alignment of the C2–O bond and C5–SF\(_5\) bonds in either intermediate zwitterions \(I_1\) and \(I_2\) (Scheme 3) is consistent with the profound dipolar influence of the SF\(_5\) group. The greater congestion of \(I_1\) that results from the aforementioned inward turned methyl group is reflected by the 4.9 kcal/mol greater stability of \(I_2\) relative to \(I_1\) (Fig. 7). Even though the TS\(_1\) and TS\(_2\) energies differ by only 800 cal, the barrier to the cyclization of \(I_1\) is 7.0 kcal/mol while the barrier for \(I_2\) to cyclize is 11.1 kcal/mol (see Fig. 6, TS\(_1\) and TS\(_2\)).

It is hypothesized that competing with the slower cyclization of the more stable \(I_2\) is formation of the enamine 10 by intramolecular proton transfer. The conformation of \(I_2\) places the reactive nucleophilic carbon in relatively close proximity to the acidic α-proton attached to the pentafluorosulfanylated carbon (Scheme 4). The depletion of \(I_2\) would result in a further reduction in the yield of \(l,u\)-11.
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Fig. 7: Computed reaction profile for the [2+2] cycloaddition reaction of (R)-4b with azidoketene in dichloromethane at the (SM8)M06-2X/6-31+G(d,p) level of theory.

Scheme 3: Effect of intermediate conformation on reaction topicity. For simplicity only the reactivity of (R)-4b is shown however the reaction will follow a similar path for (S)-4b. From Fig. 3 it is apparent that only a single pair of diastereomers of 9b is favored. In all cases the Re,Re or Si, Si ring closure step is consistent with conrotatory ring closure and our single crystal X-ray diffraction studies.

Experimental

General Methods. All reactions were carried out under an argon atmosphere. Reagents were purchased from commercial sources and used without further purification. All solvents were purified by standard methods and freshly distilled under argon. A Bruker 400 MHz spectrometer was used to record the 1H (400 MHz), 13C (100 MHz), and 19F (376
MHZ) spectra for all prepared compounds. All chemical shifts are reported relative to the residual signal of CDCl3 (H, δ = 7.24; 13C, δ = 77.00) or CD2Cl2 (H, δ = 7.15; 13C, δ = 128.00). All 13C NMR spectra were acquired in proton-decoupled mode. Chemical shifts in 19F NMR spectra are reported relative to the resonance assigned to CFCl3 (δ = 0.00). Thin layer chromatography was performed with silica gel F254 adsorbent on 0.2 mm thick plastic-backed plates. The chromatograms were visualized under ultraviolet light at 254 nm, followed by staining with an aqueous solution of KMnO4 followed by heating. Flash column chromatography was performed by the method of Still77 using 70-230 mesh silica gel 60. High-resolution mass spectra were acquired using a JEOL Accu-TOF DART mass spectrometer in negative ion mode.

Reaction profile calculations for the Staudinger reaction of azidoketene and (R)-4e were performed at the M06-2X/6-31+G(d,p) level of theory to ensure the optimized structures were either minima (with no negative vibrational frequencies), or in the case of transition states, maxima (with one negative vibrational frequency).

Preparation of 2-Pentafluorosulfanyl Aldimines. To a 25 mL round-bottom flask with a male 14/20 joint equipped with a magnetic stirring bar was added approximately 0.6 g of magnesium sulfate. The flask, Schlenk filter, and 25 mL two-neck round bottom flask equipped with a second magnetic stirring bar were dried in an oven at 150 °C for 2 hours and then allowed to cool to room temperature in a desiccator. Once cooled, the aldehyde (ca. 1.0 mmol) was added as a dichloromethane solution followed by allylamine (2 mL, 0.5 M, 1.0 mmol) in dichloromethane. The reaction mixture was stirred at room temperature for about 6 hours, after which time another 2 mL aliquot of allylamine in dichloromethane was added to the mixture. The mixture was then stirred overnight at room temperature to afford a dichloromethane solution containing the imine.

Preparation of 2-Pentafluorosulfanylaldimines (rac-4a). Orange-colored solution; 82% conversion by 19F NMR. 19F NMR (CDCl3) δ 82.0 (q; J = 146.5 Hz; 1F), 69.1 (dt; J = 146.5 Hz, 7.7 Hz; 4F). N-(2-Pentafluorosulfanylthiylidene)-3-aminoprop-1-ene (rac-4b) and N-(2-Pentafluorosulfanylprop-1-enyl)-3-aminoprop-1-ene (5b). Orange-colored solution; 70% conversion to imine rac-4b and 19% conversion to enamine 5b by 19F NMR. 19F NMR (CDCl3) δ 93.7 (q; J = 148.8 Hz; 1F; 5b), 83.7 (q; J = 143.3 Hz; 1F; 4b), 65.5 (d; J = 148.8 Hz; 4F; 5b), 58.8 (dd; J = 143.4 Hz, 4.4 Hz; 4F; 4b).

Preparation of 2-Pentafluorosulfanyl-3-aza-dizido-β-lactams. A solution of azidoacetyl chloride (ca. 0.72 g, 6 mmol, 5 eq.) in dichloromethane (5 mL) was introduced to the round-bottom flask containing apparatus described above followed by a solution of triethylamine (ca. 0.61 g, 6 mmol, 5 eq.). On completion of triethylamine addition, the resultant mixture was allowed to stir 5 minutes at −78 °C at which time the filtered imine solution was directly introduced to the round bottom flask. The reaction was then allowed to warm to room temperature with stirring overnight.
The reaction was quenched with 10 mL saturated sodium bicarbonate solution, and the organic phase was separated from the aqueous phase. The aqueous phase was extracted with three 10 mL portions of dichloromethane. The organic fractions were combined and then washed with brine (3 x 10 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated by rotary evaporation to afford the crude product. Purification of the product was accomplished by flash column chromatography using silica gel and 12:6:1 dichloromethane/hexane/ethyl acetate as the eluent.

**Notes and references**


**Conflicts of interest**

There are no conflicts to declare.

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**Notes and references**


