Carbon Bond Catalysis: Dialkyl Sulfates, Alkyl Sulfonates and Alkyl Halides as Catalysts in Acetal Forming and Related Reactions

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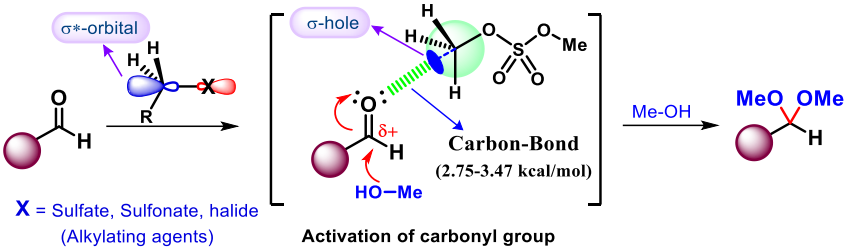
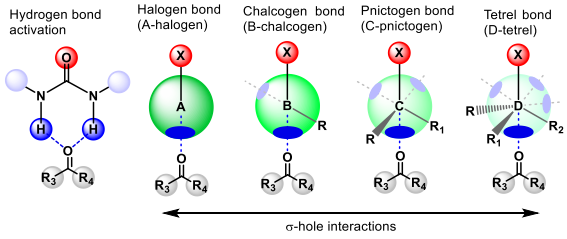


ABSTRACT: This study demonstrates a previously unexplored facet of sp^3-carbon electrophiles (or alkylating agents): their potential for catalytic applications through carbon-bond interactions. In contrast to their classical S_N1 and S_N2 reactions, we present an alternate perspective, the catalytic nature of alkyl electrophiles through noncovalent interactions (NCIs). The involvement of NCIs by carbon electrophiles (possessing polar Csp^3-X bonds) in stabilizing conformations of small molecules and biomolecules has recently been discovered. Nevertheless, their catalytic role in activating small molecules has not been observed. As the "X" group evolves into an effective leaving group, carbon electrophiles develop strong positive potentials on the carbon surface (σ-hole). However, small atomic size and steric congestion resulting from the presence of four groups around the carbon atom pose challenges in establishing strong σ-hole interactions with nucleophilic acceptors. This unique behavior of alkyl electrophiles has deterred chemists from exploring their potential as catalysts in chemical transformations. In groundbreaking revelation, we demonstrate for the first time that alkyl electrophiles function as Lewis acid catalysts in activating carbonyls for acetal formation and related reactions through NCIs. We meticulously chose a range of alkyl electrophiles and discovered a striking correlation between their molecular electrostatic potential (MEP) surface energies and their catalytic efficacy in acetal-forming reactions. Our comprehensive approach, which encompassed both experimental and theoretical investigations, provided robust support for the catalytic potential of alkyl electrophiles through non-covalent carbon bond interactions.

INTRODUCTION: Catalysis employing diverse organic small molecules is experiencing a notable upsurge, encompassing an increasingly comprehensive array of chemical transformations. These small molecules facilitate catalysis by engaging in covalent interactions, as well as an assortment of attractive noncovalent interactions (NCIs), such as H-bonding, dipole-, π-, σ-hole interactions, etc.[1] Generally, the stabilization of transition states through attractive NCIs plays a pivotal role in catalysis by lowering the kinetic barriers to reactions.[2] Heavier elements spanning group 13 to 17 engage in σ-bond catalysis[3] through NCIs, which serves as a counterpart of Lewis acid catalysis and operates solely through Coulombic interactions.[4] Analogous to hydrogen bonding[5], heavier elements within halogens,[6] chalcogens,[7] and pnictogens[8] activate small molecules by utilizing σ-holes to promote catalysis. Similarly, group 14 elements engage in NCIs through σ-holes, referred to as tetrel bonds.[9] Carbon is the most abundant element in biomolecules, materials, and medicine and the only neutral element (unlike acidic boron or basic nitrogen, oxygen, and fluorine in its hydride form) of second-row elements which can show both positive and negative charge density in its surface; yet, until 2013, the NCIs exerted by carbon electrophiles through σ-holes were entirely ignored.[10]

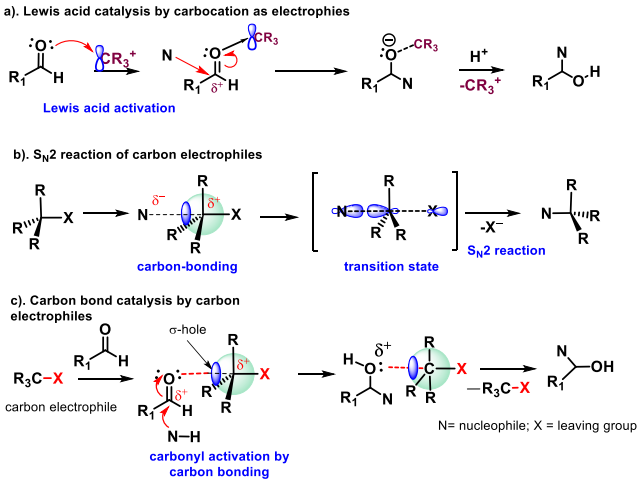
Figure 1: Representative structures for activation of carbonyl group by hydrogen bond and σ-hole interactions.



The strength of tetrel bonds is comparable to that of hydrogen bonds and other σ-hole interactions. However, catalysis by "carbon bonds" (an NCI between acceptor **A** and a σ-hole on the electrophilic carbon, **X**–**C**···**A**; **X** = polar group) has never been reported. The polarizability (size) of the acceptor atom generally plays a crucial role in determining the potential of the σ-hole. This potential strengthens from top to bottom, and from left to right in the periodic table.[11] As depicted in Figure 1, the transition from group 17 to group 14 leads to an escalation in σ-hole strength and an augmentation in the number of neighboring groups enveloping the donor atoms. Carbon, being relatively

small and less polarizable in contrast to Si, Ge, and Sn, encounters challenges when enclosed by four groups. Consequently, establishing robust interactions becomes more intricate for nucleophiles. This results in carbon bond interactions being notably weaker compared to other Tetrel-bonds. Arunan and Bundhun independently reported the existence of carbon bonds following calculations involving interactions between polar $C_{(SP3)}$-X groups and acceptor atom **A** through n→σ* interactions.[10] This breakthrough led to the emergence of numerous studies that delve into the importance of carbon bonds across various domains, including small molecules, proteins, and chemical reactions.[12] Notably, carbon bonds have demonstrated their essential role in stabilizing protein foldings,[13] ligand-acceptor interactions[12] and influencing small molecule conformations,[14] and even directing S_N2 reactions, as evidenced in a study by Grabowski.[15] However, these studies are preliminary in nature, and further extensive research is needed to gain a comprehensive understanding of the role of carbon bonds in correlation between structure and function, protein-ligand interactions, as well as enzymatic and non-enzymatic catalysis.

Scheme 1: Possible reaction paths catalyzed by different carbon electrophiles.



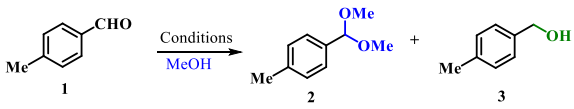
Positively charged carbon electrophiles, especially those that are sterically crowded and persistent carbocations, generate Lewis acid adducts or frustrated Lewis pairs with nucleophilic groups.[16] These Lewis acidic interactions lead to the activation of small molecules to drive catalysis of various chemical reactions (Scheme 1a).[17] On the other hand when dealing with neutral carbon electrophiles, they participate in S_N2 reactions. initially, the incoming nucleophile establishes attractive NCIs with the electrophilic carbon, which further strengthens, leading to the formation of a transition state.[15] As the acceptor becomes strongly nucleophilic, the transition state results in the formation of new covalent bond (Scheme 1b), while the X-group is released.

In contrast, a different scenario arises when the nucleophile is weaker than the leaving group. In this situation, the initial attractive interactions do not lead to the transition state. Instead, these attractive electrostatic interactions induce polarization in the acceptor, as observed in the case of carbonyl groups activated through n→σ* interactions. This polarization facilitates nucleophilic addition at the carbonyl carbon (Scheme 1c). This phenomenon is conceptually similar to the Lewis acid activation of a carbonyl group but is distinguished by the presence of a σ-hole on carbon, a novel and previously unknown feature. Herein, we present, for the first time, catalytic applications of neutral carbon electrophiles, including halo alkanes, dialkyl sulphates, and alkyl sulfonates for transforming carbonyl compounds into acetals and related compounds. These carbon electrophiles activate small molecules through unique carbon bond interactions, this is a novel discovery previously not reported. Our investigation relies on extensive NMR studies, controlled experiments, and computational methods to elucidate the underlying mechanisms of these acetal forming reactions.

RESULTS AND DISCUSSION:

Unexpected formation of 3-methoxy benzaldehyde dimethyl acetal **15** in a reduction reaction of 3-methoxy benzaldehyde (see SI, S5)[18] with $NaBH_4$ marked the beginning of this investigation. The underlying source of the reaction was later discovered to be the presence of trace amounts of dimethyl sulfate (DMS) in the reaction mixture. Previously, two individual groups reported acetalization of aldehydes using DMS. Schmitz, proposed DMS as a methylating agent for aldehyde *bis*(olate), a hypothetical intermediate expected to be generated from the aldehyde in an alkaline solution.[19] Contrariwise, Langvad emphasized, DMS acted as a water scavenger; it hydrolyzed with in situ liberated water to produce H_2SO_4.[20] To clarify these conflicting hypotheses, we conducted an extensive investigation of the reaction. As outlined in Table 1, (also see SI, S6) the acetalization of 4-methylbenzaldehyde could indeed be achieved with just a catalytic amount of DMS (5 mol%) to give product **2** in a remarkable 94% yield (entry 4, Table 1). Our discoveries not only refute the prior hypotheses but also, for the first time, establish that DMS operates as a catalyst, employing a novel catalytic mechanism that was subsequently verified as a unique NCI of carbon electrophile.

Table 1: Optimization for acetalization[a].



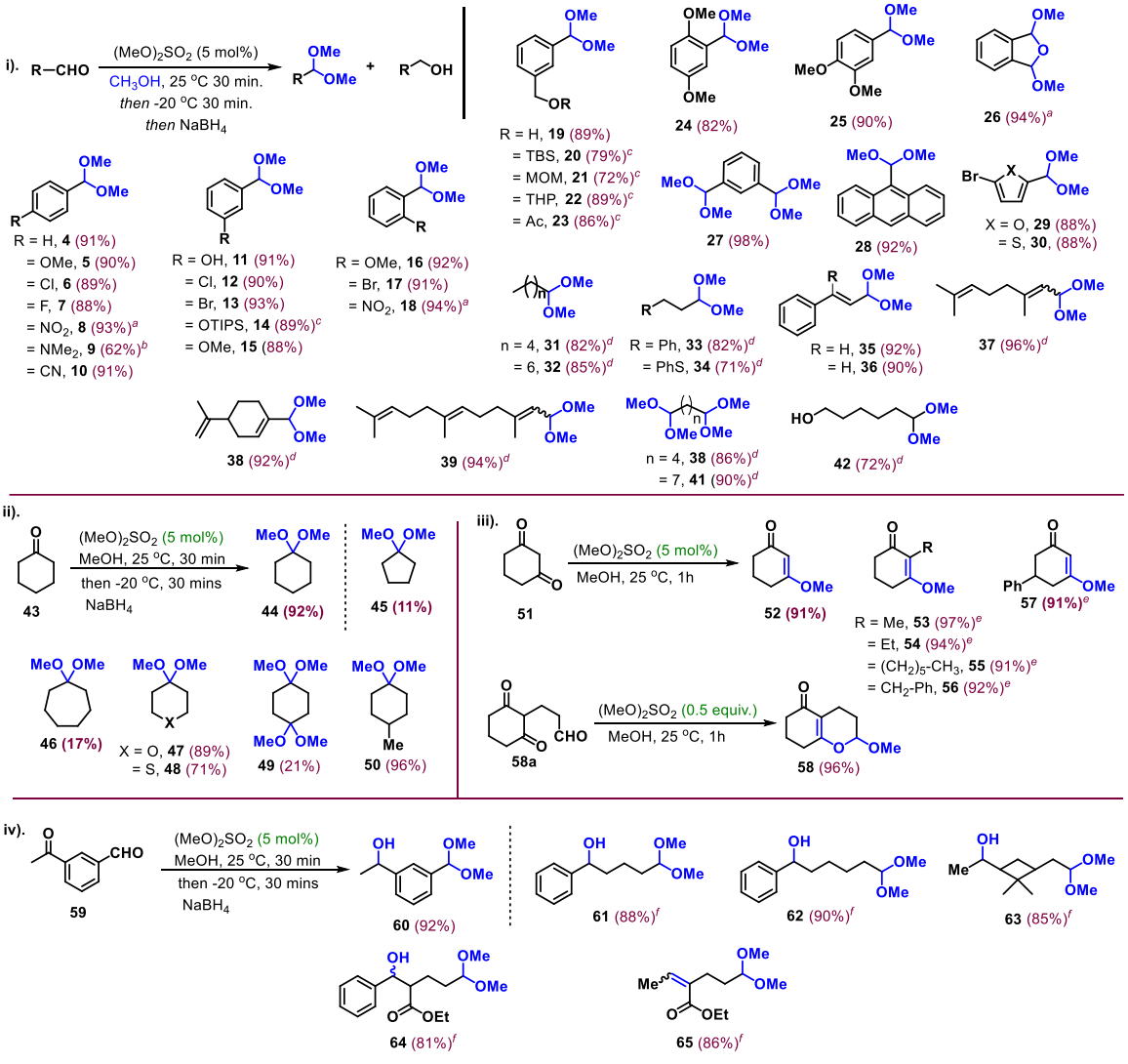
Entry	Conditions	Yield [1:2:3][b]
1.	$(MeO)_2SO_2$ (0.2 equiv.), 30 min. $NaBH_4$ (0.2 equiv.), 25 °C	0:91:9
2.	$(MeO)_2SO_2$ (0.1 equiv.), 30 min. $NaBH_4$ (0.2 equiv.), 25 °C	0:92:8
3.	$(MeO)_2SO_2$ (0.05 equiv.), 30 min. $NaBH_4$ (0.1 equiv.), 25 °C	0:94:6
4.	$(MeO)_2SO_2$ (0.02 equiv.), $NaBH_4$ (0.1 equiv.), 30 min, 25 °C	0:83:17
5.	$(MeO)_2SO_2$ (0.2 equiv.), Et_3N (1 equiv.), 30 min, 25 °C	9:91:0[f] 100:0:0[g]
6.	$(MeO)_2SO_2$ (0.2 equiv.), NaOH (1 equiv.), 30 min, 25 °C	11:89:0[f] 100:0:0[g]
7.	$(MeO)_2SO_2$ (0.5 equiv.), DTBP (0.1 equiv.), 4 h, 25 °C	30:70:0
8.	$(MeO)_2SO_2$ (0.5 equiv.), Proton sponge (0.1 equiv.), 25 °C, 2 h	56:44:0
9.	$(MeO)_2SO_2$ (0.5 equiv.), DTBP (0.5 equiv.), 4 h, 25 °C	28:72:0

10.	CH_3OSO_3H (0.05 equiv.), 30 min, 25 °C	17:83:0
11.	CH_3OSO_3H (0.02 equiv.), 30 min, 25 °C	36:64:0
12.	CH_3OSO_3H (0.2 equiv.), DTBP (0.25 equiv.), 24 h, 25 °C	100:0:0

[a] Reactions were carried out with 2.5 mmol **1**; [b] Yields were calculated by ^{1}H-NMR using 1,1,2,2-tetrachloroethane as internal standard.

Further experiments revealed that the reaction is instantaneous; requiring as little as 2 to 5 mol% DMS. The most significant advantage of this approach lies in its compatibility with laboratory-grade methanol, making it amenable to open flask procedures without the necessity for dehydrating agents or azeotropic techniques. This method is scalable to multigram quantities (achieving **4** in 86% yield in a 50 g batch) and is compatible with various acid-sensitive protecting groups. Additionally, the in-situ reduction of unreacted aldehyde presents the advantageous prospect of facilitating the easy separation of the acetal from more polar alcohol byproduct.[21]

Scheme 2: DMS catalyzed acetal, ketal, enol ether formations and a selective one-pot aldehyde protection and ketone reduction.



i). Reactions were conducted with aldehyde (5 mmol), DMS (5 mol%) and $NaBH_4$ (20 mol%); [a] 3 hours; [b] DMS (50 mol%); [c] 0 °C, 3 h; [d] DMS (20 mol%), 3 h; ii). Ketone (5 mmol), DMS (5 mol%) and $NaBH_4$ (20 mol%); iii). diketone (5 mmol), and DMS (5 mol%); [e] diketone (5 mmol), DMS (50 mol%) at 60 °C; iv). ketoaldehyde (2.5 mmol) DMS (5 mol%) and $NaBH_4$ (1.2 equiv.); [f] ketoaldehyde (2.5 mmol) DMS (20 mol%) and $NaBH_4$ (1.2 equiv.).

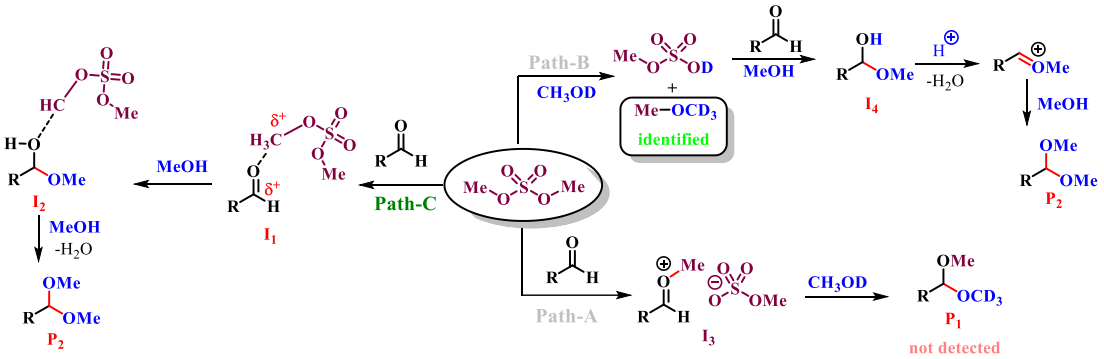
As outlined in Scheme 2 the method is widely applicable for a variety of aromatic, hetero aromatic, aliphatic, and α,β-unsaturated aldehydes to provide corresponding dimethylacetals (**4** to **42**) in yields ranging from 64 to 94%. Several acid-sensitive protecting groups, such as silyl ethers, MOM, THP, and acetate remained intact (**14**, **20**–**23**). The yields of these compounds were affected when the reactions were performed under standard conditions. Nevertheless, using anhydrous methanol in a controlled environment at 0 °C for 3 hour resulted higher yields. Compounds containing amine substituents did not provide corresponding acetals due to N-methylation by DMS. Notably, 4-N,N-dimethylamino benzaldehyde was the only aldehyde with an amine substituent that reacted with 0.5 equiv. of DMS, providing acetal **9** in moderate yields of 62%. Phthalaldehyde provided oxalane **26** in 94% yield, whereas isophthaladehyde

gave *bis*-acetal **27** in 98% yield. Conjugated aldehydes produced corresponding acetals without any Michael addition product or unwanted cyclization reactions (**35** to **39**).

The conversion of ketones into their corresponding ketals exhibits limitations, with only 6-membered cyclic ketones reacting successfully with methanol in the presence of 5 mol% of DMS. Notably, the reaction of cyclohexanone and its derivatives yielded ketal products (compounds **44**, **52** to **55**) in good yields. The underlying reason for this selectivity remains unknown and has been a surprising encounter.[22] Furthermore, an important transformation involves the conversion of 1,3-diketones into their corresponding β-methoxy enones. When 1,3-cyclohexadiones reacted with methanol in the presence of catalytic DMS, they furnished corresponding 3-methoxy cyclohexenone derivatives (compounds **57** to **62**) in yields exceeding 90% (Scheme 2iii). Additionally, compound **63a**, when subjected to a reaction with methanol, yielded bicyclic acetal **63** in a high yield of 96%.

Based on the foregoing data, it is evident that aldehydes have higher propensity than ketones to undergo acetal formation. This distinct reactivity bias has enabled us to implement a tandem process involving aldehyde protection and ketone reduction in a one-pot synthesis (Scheme 2iv). In comparison to prior methods that relied on lanthanide metals for chemoselective ketone reduction, this one-pot procedure for protection and reduction offers several advantages, including milder reaction conditions, faster reaction rates, superior selectivity, and higher yields.[23] To illustrate this methodology, the transformation of 3-acetylbenzaldehyde **64** is exemplified. It underwent acetalization in the presence of methanol and DMS, followed by $NaBH_4$ reduction, resulting in the formation of hydroxy acetal **65** in a commendable yield of 92%. Similarly, other ketoaldehydes underwent selective conversion to their respective hydroxy acetals **66** to **70**, consistently yielding excellent results. Notably, aldehydes containing β-keto ester functionality displayed remarkable chemoselectivity for ketone reduction, ultimately affording acetals **69** and **70** with high efficiency.

Scheme 3: Possible mechanistic pathways; Path-A: electrophilic activation by methyl transfer; Path-B: in situ formation of MBS and a Brønsted acid catalysis; Path-C: electrophilic activation of carbonyl through noncovalent interactions.



Following the successful validation of our method, our attention turned towards elucidating the underlying mechanism. As mentioned earlier, the catalytic behavior of dialkyl sulfates has not been previously documented. Upon meticulous analysis of the experimental outcomes, we hypothesized the existence of three distinct reaction pathways that could be employed with dimethyl sulfate (DMS) serving as the catalyst. As illustrated in Figure 2, extensive time-dependent NMR studies were employed to substantiate the putative mechanism and exclude alternative competitive pathways (see, SI S8-S12). Initially, one potential pathway considered was the electrophilic O-methylation of the carbonyl oxygen by dimethyl sulfate (DMS), resulting in the formation of a methoxonium ion (**I**$_3$), which, upon the addition of methanol (MeOH), would yield dimethyl acetal (**P1**). However, the NMR experiment conducted on compound **1** in CD_3OD solvent, utilizing both catalytic and stoichiometric levels of DMS, did not yield any mixed acetal **P**$_1$ (Figure 2a).[24] Instead of carbonyl methylation, it was observed that solvent methanol underwent methylation, resulting in the production of a mixed dimethyl ether ($CD_3OC\underline{\mathbf{H}}_3$ at δ 3.31 ppm; Figure 2a, see SI, S8) and methyl bisulfate (MBS) ($C\underline{\mathbf{H}}_3OSO_3H$, δ 3.38 ppm).[25] These results prompted us to reevaluate the mechanism, considering the possibility of Brønsted acid catalysis, given the significant acidity of MBS (pKa = –3.4±0.15).[26] Even in trace amounts, MBS has the capacity to catalyze the acetalization process.[27]

Furthermore, a series of carefully designed controlled experiments were conducted with utmost care to identify the primary catalytic species responsible for the reaction. In an alternative NMR experiment carried out at 0 °C, it was observed that the methanolysis of DMS occurred at a significantly slower rate; after 1 hour, the DMS-to-MBS ratio was 273:1, calculated from NMR experiment (see SI, S8). In contrast, the acetalization reaction was remarkably rapid, achieving **2** in a 77% yield within a mere two minutes of reaction initiation.

In a second set of controlled experiments, a base was introduced into the reaction medium to effectively eliminate the in-situ proton, thus allowing for an assessment of the catalytic efficacy of DMS in isolation. Notably, the addition of sterically hindered bases such as 2,6-di-*tert*-butylpyridine (2,6-DTBP), or proton sponge, led to the formation of the desired product **2** in a respectable yield (entries 7-9, Table 1).[28] On the other hand, when Methyl bisulfate (MBS, 2 mol%) was employed as a catalytic agent, a substantial 64% yield of **2** was achieved within a 30-minutes (entry 10, Table 1).[29] However, the intrigue deepens when the same experimental procedure was replicated, utilizing a mixture of 0.2 equiv. of MBS and 0.25 equiv. of 2,6-DTBP (entry 12, Table 1). This experiment resulted in the quantitative recovery of the starting aldehyde. Collectively, these experiments serve to unequivocally exclude Brønsted acid catalysis

via the involvement of in situ protons as a governing mechanism (Scheme 2, path B). Instead, they illuminate the emergence of a novel catalytic pathway primarily orchestrated by dimethyl sulfate alone. This pathway hinges on Lewis acid interactions facilitated by the electrophilic methyl group of DMS.

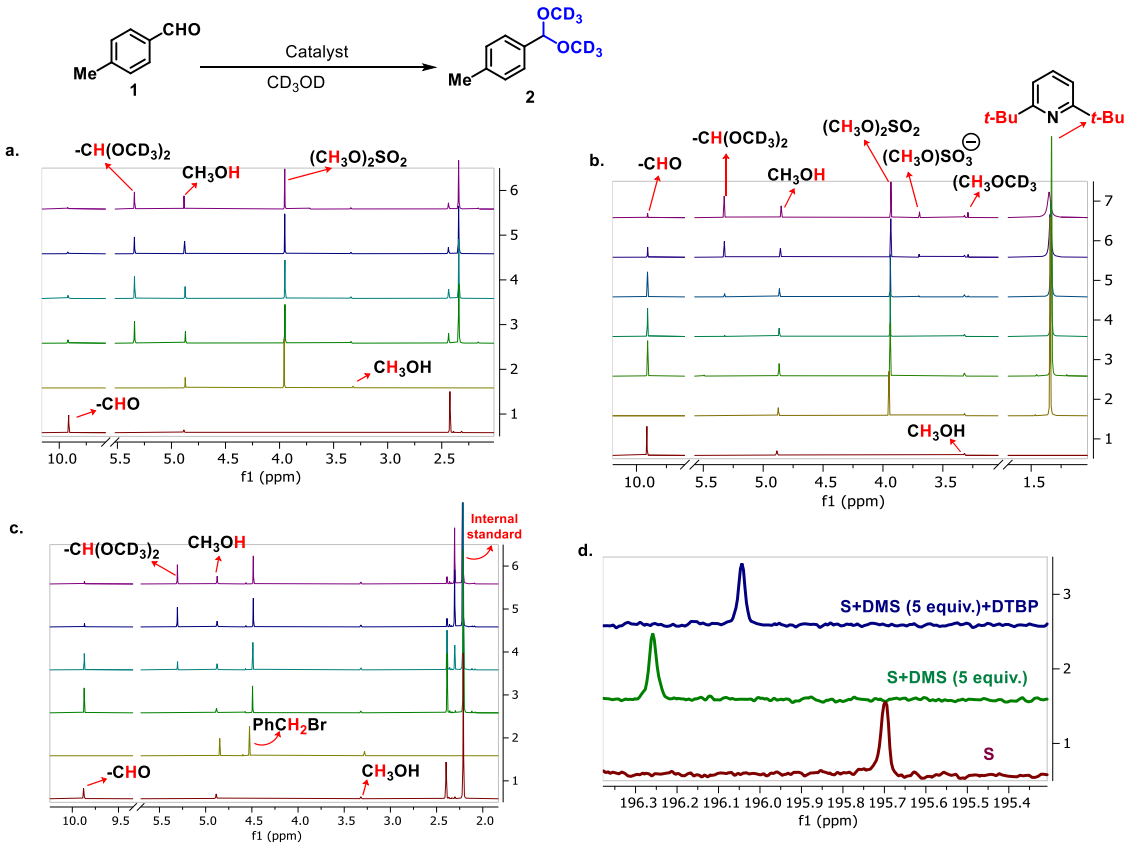


Figure 2: a. ^{1}H-NMR reactions of **1** with DMS (20 mol%) in CD_3OD at 22 °C, internal standard $(Cl_2CH)_2$; b. same reaction using DTBP; c. ^{1}H-NMR reactions of **1** with benzyl bromide (50 mol%) in CD_3OD at 22 °C, internal standard mesitylene; d. ^{13}C-NMR study of benzophenone (**S**) with DMS and DTBP in C_6D_6 at 22 °C.

To gain a deeper understanding of the Lewis acidic nature exhibited by alkyl electrophiles, we have delved into a recently emerging concept involving a novel noncovalent interactions of carbon electrophiles with a acceptor by σ-holes of carbon termed "carbon-bond." In our pursuit of comprehension, we employed computational calculations utilizing the Gaussian16 software.[30] Initially, we conducted molecular surface electrostatic potential (MEP) calculations for the DMS (entry 5, Tables 2i). Our computational models unveiled a σ-hole characterized by a positive potential energy of 25.8 kcal/mol on the surface of the methyl carbon atom within DMS. Notably, this σ-hole is precisely aligned with the σ*-orbital of the carbon oxygen (C-O) bond (Figure 3a). Furthermore, a stimulating observation was made regarding one of the hydrogen atoms within the methyl group, which exhibited a similarly elevated positive potential energy of 26.2 kcal/mol. This unusual positive charge potential on a single hydrogen atom can be attributed to stereoelectronic effects. Specifically, the alignment of dipoles towards the sulfate group results in depleted electron regions surrounding the anti-hydrogen position (Figure 3e).[31]

As depicted in Figures 3d, the carbonyl oxygen atom of acetaldehyde engages in an interaction with the σ-hole of a methyl group within dimethyl sulfate. Notably, the intermolecular distance ($H_3C\cdots O{=}C$) for the complex was 3.11 Å, which was observed to be shorter than the sum of the normalized van der Waals radii for carbon (C) and oxygen (O) atoms (3.225 Å). This observation provides compelling evidence of a favorable interaction within this system. The computed interaction energy for the DMS-acetaldehyde complex was found to be 3.03 kcal/mol (Table 2ii). Further insight into these weak interactions was gained through the visualization of non-covalent interactions using the Multiwfn tool.[32] This analysis confirmed the presence of a green isosurface between the methyl carbon center and the carbonyl oxygen (Figures 3e), reinforcing the notion of these subtle interactions.[33] Additionally, natural bonding orbital (NBO)[34] analysis indicated an interaction energy of [LP(O)→σ*(H_3C-O)] with a value of 0.83 kcal/mol (also see SI, S14). We observed non-covalent interactions between dimethyl sulfate (DMS) and the carbonyl group of benzophenone through ^{13}C-NMR analysis in C_6D_6 solvent (refer to Figure 2d). The carbonyl signal of benzophenone exhibited a shift from δ 195.7 to 196.3 ppm upon the addition of DMS, indicating a distinct interaction. Conversely, a similar experiment conducted in the presence of DTBP resulted in a slight downfield shift to 196.1 ppm, offering clear confirmation of the Lewis acid interaction between dialkyl sulfate and the carbonyl group.

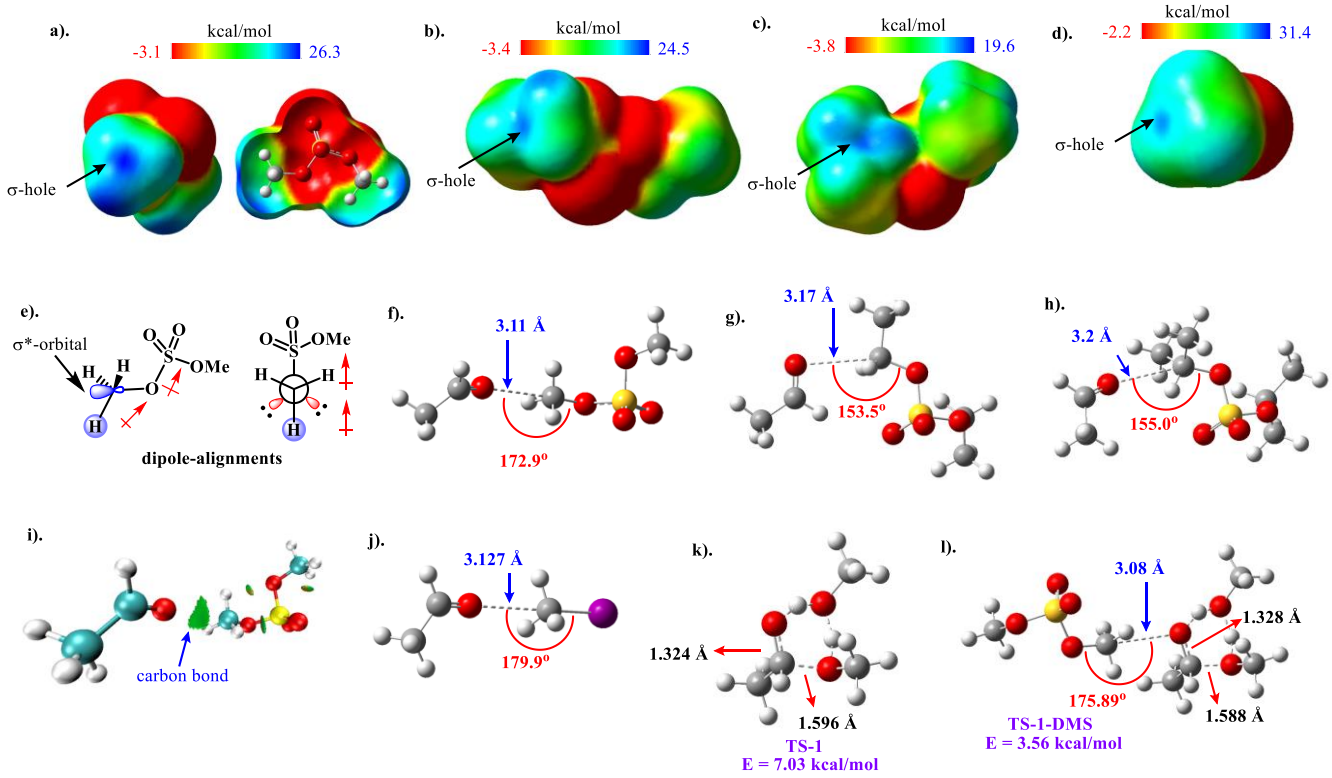


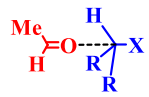
Figure 3: a). Molecular electrostatic surface energy (MEP) potential of DMS; b). MEP of diethyl sulfate (DES); c). MEP of diisopropyl sulfate (DIPS); d). MEP of methyl fluoride; e). dipole-alignments in DMS; f). interactions between acetaldehyde and DMS calculated at UMP2-FC/6311G(d,p); g). interaction between acetaldehyde and DES calculated at UMP2-FC/6311G(d,p); h). interaction between acetaldehyde and DIPS calculated at UMP2-FC/6311G(d,p); i). NCI plot of DMS and acetaldehyde; j). interactions between acetaldehyde and methyl iodide calculated at UMP2-FC/6311+G(3df,2p), def2TZVP used for iodine; k). Transition state (TS-1) of acetalization (uncatalyzed) calculated at UMP2-FC/6311G(d,p)/SMD(methanol); l). stabilization of TS-1 by DMS calculated at UMP2-FC/6311+G(3df,2p)/SMD(methanol). Structures were visualized and MEPs were calculated in GaussView 6.[35] MEPs were calculated at 0.001 a.u. isosurface of electron density. Color coding of Multiwfn tool, attractive interactions: blue-strong, green-weak, and repulsive interactions: red-strong, yellow-weak.[33] The gradient cut-off is σ=0.5 au, and color scale is -0. 04 < ρ < 0.02 a.u.

Table 2: MEP energies of different electrophiles and bond distance, interaction energy, bond angle, and NBO interaction with acetaldehyde.

i). MEP-surface values[a].

Sl. No.	Electrophiles	Vmax (kcal/mol) 6-311+G (3df,2p)	aug-cc-PVTZ
1.	Methyl Fluoride	22.5	22.97
2.	Methyl Chloride	19.3	19.4
3.	Methyl Bromide	18.5	18.0
4.	Methyl Iodide	14.9[b]	14.4[b]
5.	Dimethyl sulfate	25.8	25.5
6.	Methyl mesylate	22.8	22.5
7.	Methyl Tosylate	19.95	19.7
8.	Methyl Triflate	33.7	33.8
9.	Diethyl sulfate	21.6	-
9.	Diisopropyl sulfate	21.1	-

ii). Interaction between electrophiles and acetaldehyde[c].



	CH_3-OSO_3Me	$MeCH_2$-OSO_3Et	Me_2CH-OSO_3*i*-Pr	CH_3-I[b]
Bond Distance (Å)	3.11 Å	3.17 Å	3.2 Å	3.24 Å
Interaction Energy (kcal/mol)	-3.03	-4.62	-4.07	-2.12
Bond Angle (∠O···CH_3-X)	172.9°	153.5°	155.0°	179.6°
NBO Energy [LP(O) → σ*(H_3C-X)]	0.83	0.72	0.47	0.24

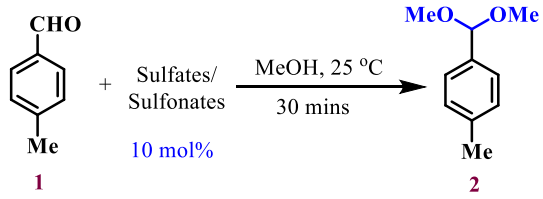
[a] Structures are optimized at UMP2-FC/6311+G(3df,2p) and UMP2-FC/aug-cc-PVTZ level of theory in Gaussian16; MEP energy in kcal/mol. [b] For iodine def2-TZVP basis set was used; [c] Structures were optimized at UMP2-FC/6311G(d,p) level of theory.

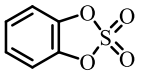
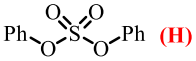
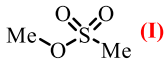
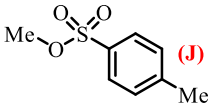
In light of our comprehensive examination of both experimental and theoretical observations, we put forth a third plausible mechanism, illustrated in Scheme 3, path-C. This mechanism posits that attractive carbon bond interactions inducing polarization in the carbonyl group via complex **I_1**. This was clearly supported by the computational models as depicted in Figure 3f (see SI, S16). Where, aldehyde group is activated by DMS, and methanol is added to electrophilic carbon, involving a six membered transition state, yielding a hemiacetal. It's worth noting that hemiacetal formation is inherently reversible. However, dimethyl sulfate (DMS) plays a crucial role in promoting the forward reaction by engaging in similar carbon bond interactions through complex **I_2** (see SI, S16). Consequently, this results in the formation of dimethyl acetal as the end product of the reaction.

Furthermore, to generalize this concept, MEP energies for different dialkyl sulfates, methyl sulfonates and alkyl halides were computed (Table 2, also see SI, S16). In the case of halides, electronegativity influences the surface potentials, with methyl sulfonates exhibiting the highest MEP values, particularly with strongly electron withdrawing groups like methyl triflate. Similarly, dimethyl sulfate shows a significantly positive potential on the methyl surface, surpassing that of methyl halides and methyl- mesylate and tosylates. Meanwhile, higher alkyl sulfates exhibit little lower positive potential on carbon directly attached to the sulfate group. Interestingly, in the case of diethyl, diisopropyl sulfates, the charges disperse across adjacent carbons, primarily through the C-H bonds (Figure 3b and 3c).

Table 3: Acetal formation with different dialkyl sulfates, methyl Sulfonates, and halo alkanes.

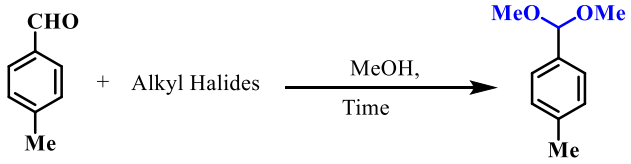
i). Acetal formation with different dialkyl sulfates and methyl Sulfonates[a].



Sl. No.	Sulfates/Sulfonates	Yield[b]
1.	$(MeO)_2SO_2$ **(A)**	89%
2.	$EtO)_2SO_2$ **(B)**	78%
3.	$(i\text{-}PrO)_2SO_2$ **(C)**	65%
4.	$(n\text{-}BuO)_2SO_2$ **(D)**	49%
5.	 **(G)**	0
6.	 **(H)**	0
7.	 **(I)**	50%
8.	 **(J)**	34%

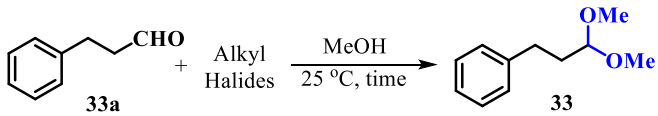
[a]All Reactions were carried out in 2.5 mmol of aldehyde **1** in methanol at 25 °C. [b]Yields calculated based on crude NMR analysis, taking 1,1,2,2-tetrachloroethane used as internal standard; [c] isolated yields; [d] aldehyde 33a was subjected for acetal formation.

ii). Acetal formation with different alkyl halides[a].



Sl. No.	Alkyl Halides	Catalyst loading	Time	Yield[b]
1.	CH_3I **(I)**	10 equiv.	12 h	56% (49%[c])
2.	 X= Br, **(II)**; X = I, **(III)**	0.5 equiv.	1 h	**II**= 77% (64%[c]) **III**= 74%
3.	 X= Cl, **(IV)**; X = Br, **(V)**	0.5 equiv.	**IV**= 4 h **V**= 1 h	**IV**= 47% **V**= 74%
4.	Ph−Br **(VI)**	1 equiv.	12 h	0
5.	 + 2,6-DTBP	0.5 equiv. (both)	24 h	76%

iii). Aliphatic acetal formation with different alkyl halides[d].



Sl. No.	Alkyl Halides	Catalyst loading	Time	Yield[b]
1.	CH_3I **(I)**	10 equiv.	12 h	40%
2.	 **(II)**	0.5 equiv.	3 h	49%
3.	 **(V)**	0.5 equiv.	3 h	46%

Subsequently, NCIs between sulfates **A**, **B**, **C**, and methyl iodide (**I**) with acetaldehyde were computed. As depicted in Figures 3i and 3ii, a robust correlation is evident between MEP energies of electrophiles and the bond distances between the carbonyl oxygen and electrophilic carbon. DMS exhibited the shortest distance, whereas DES and DIPS displayed higher interaction energies with acetaldehyde. As the size of alkyl groups increased, additional interactions, beyond σ-hole interactions, also came into play (see figure 3g and 3h, also see SI, S15). These secondary interactions significantly influenced the conformations of transition states, as demonstrated by the deviation in bond angles between the donor atom and acceptor C-X bond

[C=O·····C-OSO_3R]. In contrast, NBO energy analysis unambiguously reveals substantial contributions from donor carbon mainly through carbon-bond interactions [LP(O)→σ*(H_3C-O)]. Remarkably, the MEP values of various electrophiles and their NBO interaction energies exhibit a strong correlation with our experimental results regarding the catalytic efficacy of these electrophiles.

Further, we extended our investigation to encompass several higher analogs of DMS, including dialkyl and diaryl sulfates, in the context of the acetalization of aldehyde **1**. As delineated in Table 3i, compounds such as diethyl sulfate (**B**), diisopropyl sulfate (**C**), and di-*n*-butyl sulfate (**D**) exhibited the desired catalytic activity, resulting in the successful formation of the target product **2**. Intriguingly, the utilization of diphenyl sulfate (**E**) and catechol sulfates (**F**) failed to yield the desired product **2**. These experiments conspicuously underscore that the sulfate moieties themselves do not exert any catalytic influence; rather, it is the alkyl groups appended to the sulfate that play a pivotal role in catalysis. Furthermore, it is noteworthy that sulfonate esters such as methyl mesylate (**G**) and methyl tosylates (**H**) also exhibited catalytic activity in promoting the acetalization of aldehyde **1** (entries 7 and 8, Table 3i)

To harness the Lewis acidic nature of alkyl electrophiles for catalytic purposes, we systematically employed various alkyl halides, commonly utilized as alkylating agents and solvents in organic synthesis. As depicted in Table 3ii, these alkyl halides proved highly effective in catalyzing the acetalization of aldehyde **1**.[36] Notably, alkyl halides with greater polarizability demonstrated enhanced catalytic performance (entry 3, Table 3ii). Moreover, the presence of conjugation, as observed in the case of allyl and benzyl groups, further augmented the catalytic activity.[37] The acetalization of aldehydes **33a** was quite effective. In a time-dependent ^{1}H-NMR experiment of **1** in MeOH with catalytic benzyl bromide, the formation of acetal **2** was observed after 30 mins, resulting in a 35% yield and an 85% conversion after 2 h (Figure 2c). Additionally, acetalization was performed with alkyl halides and base (i.e., DTBP) resulting in the formation of acetal **2** (entry 5, Table 3).

CONCLUSIONS

In summary, we have reported novel findings that demonstrate the catalytic activity of neutral organic small molecules featuring polar $C_{(SP3)}$-X bonds through carbon bond interactions. We conducted an in-depth exploration of alkyl halides, dialkyl sulfates and alkyl sulfonates, which are commonly employed as alkylating agents in chemical reactions in industry and academia, as prospective catalysts. The carbon bond catalysis presented in our study finds application in acetalization, enolization reactions, with considerable potential for further extension to other class of reactions. We systematically assessed the σ-hole strengths of various electrophiles and estimated their interactions with carbonyl group using computational models. We are confident that this study has unvieled a new perspective for understanding the catalytic behavior of alkyl electrophiles, particularly as mild Lewis acids. These findings offer valuable insights for scientists seeking to delve deeper into the role of carbon bonds in solvent-solute interactions, the activation of small molecules for catalytic purposes, the design of novel catalysts, and investigations into enzymatic and non-enzymatic catalytic pathways. Additional studies are currently in progress to implement this novel catalysis concept in different chemical reactions, including multi-component reactions.

ASSOCIATED CONTENT

(Word Style "TE_Supporting_Informati**on"). Supporting Information**. A brief statement in nonsentence format listing the contents of material supplied as Supporting Information should be included, ending with "This material is available free of charge via the Internet at http://pubs.acs.org." For instructions on what should be included in the Supporting Information as well as how to prepare this material for publication, refer to the journal's Instructions for Authors.

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ABBREVIATIONS

CCR2, CC chemokine receptor 2; CCL2, CC chemokine ligand 2; CCR5, CC chemokine receptor 5; TLC, thin layer chromatography.

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