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Investigation of the Effect of Solvents on the Synthesis of Aza-flavanone from Aminochalcone Facilitated by Halogen Bonding

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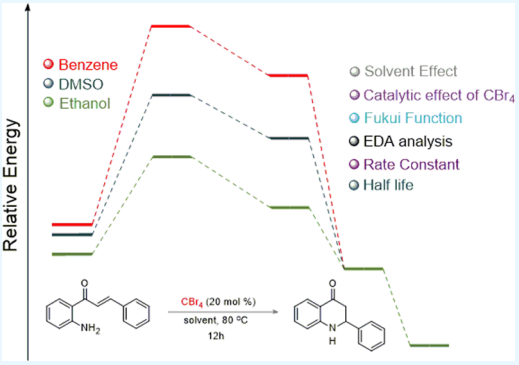
ABSTRACT: It has been recognized that CBr_4 can give rise to a noncovalent interaction known as halogen bond (XB). CBr_4 was found to catalyze, in terms of XB formation, the transformation of 2′-aminochalcone to aza-flavanone through an intramolecular Michael addition reaction. The impact of XB and the resulting yield of aza-flavanone exhibited a pronounced dependence on the characteristics of the solvent. Notably, yields of 88% in ethanol and 33% in DMSO were achieved, while merely a trace amount of the product was detected in benzene. In this work, we use a computational modeling study to understand this variance in yield. The reaction is modeled at the level of density functional theory (based on the M06-2X exchange−correlation functional) with all-electron basis sets of triple-ζ quality. Grimme's dispersion correction is incorporated to account for the noncovalent interactions accurately. Harmonic frequency calculations are carried out to establish the character of the optimized structures (minimum or saddle point). Our calculations confirm the formation of an XB between CBr_4 and the reacting species and its role in lowering the activation energy barrier. Stronger orbital interactions and significant lowering of the steric repulsion were found to be important in lowering the activation barrier. The negligible yield in the nonpolar solvent benzene may be attributed to the high activation energy as well as the inadequate stabilization of the zwitterionic intermediate. In ethanol, a protic solvent, additional H-bonding contributes to further lowering of the activation barrier and better stabilization of the zwitterionic intermediate. The combined effects of solvent polarity, XB, and H-bond are likely to give rise to an excellent yield of aza-flavanone in ethanol.



I. INTRODUCTION

Weak noncovalent interactions play a pivotal role in numerous reactions within synthetic organic chemistry. Examples include hydrogen bond (H-bond),[1,2] anion−π interaction,[3,4] cation−π interaction,[5] halogen bond (XB),[6,7] etc. The first instance of XB, a noncovalent interaction linking a halogen atom with a Lewis base, dates back to the identification of ammonium−iodine complexes in 1814.[8] Mulliken proposed that these complexes are held together by charge-transfer processes.[9,10] Theoretical investigations highlight the emergence of anisotropic electron density distribution around halogen atoms, leading to the formation of a distinctive "σ-hole"—an electropositive region along the bonding axis.[11−14] These studies also confirm a partial $n \rightarrow \sigma^*$ electron transfer in the case of XB. Within a conventional XB interaction, the halogen atom serves as a Lewis acid, receiving an electron pair from a neighboring atom. Notably, XBs appear to surpass H-bonds in both strength and directionality. The strength of XB was found to be about 10−200 kJ/mol,[15] whereas that of H-bond is about 1−40 kJ/mol.[16] The potency of an XB can be tuned by opting for an appropriate XB-donor atom (such as nitrogen, oxygen, or sulfur) possessing a specific level of polarizability. Over the past decade, XB interactions have gained prominence as novel bonding patterns. These interactions hold significance across a spectrum of chemical reactions within organic synthesis,[17] materials chemistry,[18] and biochemistry.[19]

The literature documents the catalytic influence of H-bond donor compounds extensively.[20] For example, thiourea derivatives participate in the activation of electrophilic compounds (e.g., carbonyls) through H-bonding.[21,22] In the realm of organocatalysis, XB-donor catalysts, a recent introduction, exhibit potential in diverse functional group activations.[23−25] The XB-donor catalysts provide a mild, yet precise, activation of a specific functional group. Huber and co-workers found that a number of well-known organic reactions benefit from the use of XB-donor catalysts, e.g., activation of carbonyl compounds,[26] Michael addition reaction,[24] and Nazarov cyclization reaction.[27] Saito et al. demonstrated the utilization of XB to activate iodonium ylides for cross-enolate coupling applications.[25]

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The utilization of CBr_4 as a metal-free organocatalyst has garnered substantial interest in recent years as a noteworthy substitute for transition-metal-based catalysts in organic synthesis.[28] A catalytic amount of CBr_4 was used in both the cross-dehydrogenative coupling of isocromans with aromatic ketones and the three-component reaction yielding α-amino phosphonates.[29,30] For the activation of the thioamide group in the synthesis of benzoxazoles[31] and benzothiazole derivatives,[32] XB interactions involving CBr_4 were found to be effective. Recently, CBr_4 has been employed as an XB-donor organocatalyst for synthesizing flavanones and aza-flavanones from α,β-unsaturated ketones, as depicted in Figure 1.[33] The nature of the

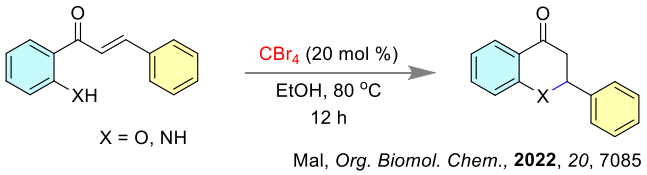

Figure 1. Activation of α,β-unsaturated ketones by the XB catalysis. (Adapted with permission from ref 33. Copyright 2022, Royal Society of Chemistry.)

solvent was found to play an essential role in the reaction. A yield of 92% of the product flavanone in ethanol (a polar protic solvent) was found to dwindle to 45% in DMSO (a polar aprotic solvent) and merely a trace amount in benzene (a nonpolar solvent).[33]

There are a number of computational studies that looked into the fundamental aspects of XB and the effect of solvents in the XB interactions. Forni et al. investigated the effect of the solvents diethyl ether and water on the I−O XB interaction in several complexes of substituted iodobenzene with formaldehyde using MP2 and density functional theory (DFT) level of theory (with several density functionals, namely, PBE, PBE0, B3LYP, BH&HLYP, M06-2X, and M06-HF).[34] All functionals, except for B3LYP, were found to describe the halogen bonding adequately in comparison to MP2. The M06-2X functional was found to be on par with MP2 to reproduce the geometrical characteristics of the halogen bonding. The XB interactions between electron-deficient iodo compounds and Lewis bases in CCl_4 and various alkane solvents were studied computationally at the level of MP2 and DFT (with 22 different DFT functionals) by Chudzinski and Taylor.[35] The results were found to agree well with the experimental thermodynamic data. Huber and co-workers used the M06-2X density functional (with Grimme's D3 dispersion corrections[36]) to computationally model the transition states in support of their proposed mechanisms for the reactions aided by XB in CH_2Cl_2 and CD_2Cl_2 solvents.[26] They used the SMD intrinsic solvation model[37] to incorporate the effect of the solvents. Breugst et al. studied four different iodine-catalyzed reactions using M06-2X functionals.[38] They explained the effect of solvation by dichloromethane in terms of the integral equation formalism of the polarizable continuum model (IEFPCM).[38]

We conducted a comprehensive experimental and theoretical investigation to explore the influence of various solvents on the activation of 2′-aminochalcone for the synthesis of aza-flavanone via an intramolecular Michael addition reaction facilitated by the XB-donor catalyst CBr_4. It is worth noting that a comparable synthetic pathway had previously exhibited considerable success.[33] The synthesis was carried out in different solvents to demonstrate the effect of the solvent on the yield. The electronic structure calculations were employed to uncover the effect of solvent vis-à-vis XB.

The next section describes our experimental and theoretical methods (Section II). This is followed by a discussion of our results (Section III). In Section IV, we summarize our results and conclude the discussion.

II. METHODS

(E)-1-(2-Aminophenyl)-3-phenylprop-2-en-1-one ("aminochalcone") was synthesized by following a standard procedure outlined in the literature.[39] A mixture of 0.179 mmol of aminochalcone and 0.034 mmol of CBr_4 in 2.0 mL of three different solvents (ethanol, DMSO, and benzene) was stirred at 80 °C for 12 h separately. Another solution of 0.179 mmol of 2′-aminochalcone in 2.0 mL of ethanol was stirred at 80 °C for 12 h. The product 2-phenyl-2,3-dihydroquinolin-4(1*H*)-one ("aza-flavanone") was isolated by using column chromatography.

In an effort to computationally analyze the reaction, we postulated that the investigated reaction follows the mechanism

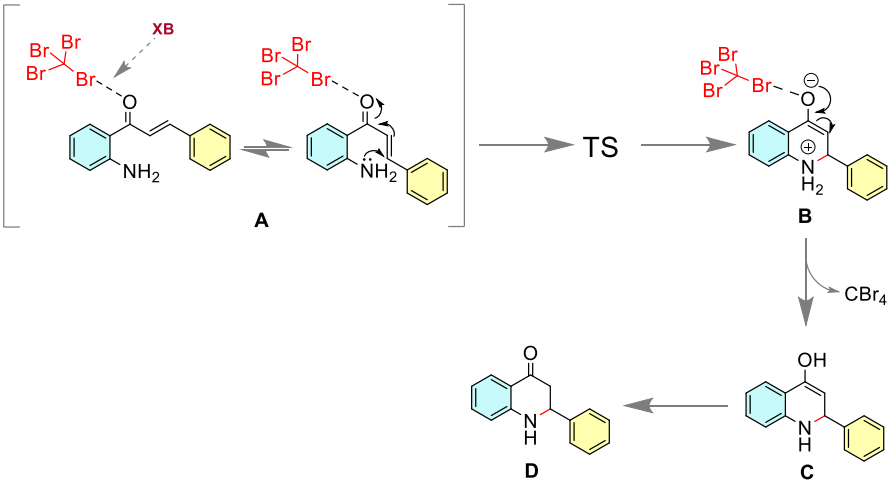

Figure 2. Proposed mechanism for the synthesis of aza-flavanone (**D**) from aminochalcone (**A**) catalyzed by CBr_4 via the transition state (**TS**), the zwitterionic intermediate (**B**), and the enolic intermediate (**C**). The halogen-bonded complexes of **A**, **TS**, and **B** are referred to as **A**-CBr_4, **TS**-CBr_4, and **B**-CBr_4, respectively, in the text.

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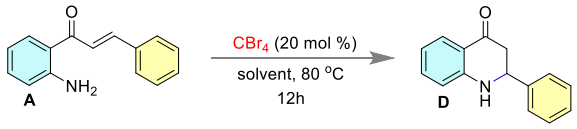
depicted in Figure 2. This mechanism aligns with the one proposed by Breugst et al. for a similar reaction.[38]

All computational model structures were optimized at their ground electronic states at the level of density functional theory (DFT) using the hybrid meta-GGA exchange−correlation functional M06-2X.[38] The D3 version of Grimme's dispersion correction was included.[36] All-electron basis sets of triple-ζ quality, namely, aug-cc-pVTZ for Br and 6-311+G(d,p) for the other atoms, were used.[38] No pseudopotential was used with a view to improve the accuracy [cf. ref 38]. Solvation effects were accounted for by the integral equation formalism of the polarizable continuum model (IEFPCM).[40] To mimic the reaction conditions closely, we used a temperature of 80 °C for the solvent model. The character of the stationary points (minimum or saddle point) was ascertained by inspecting the harmonic frequencies computed for the optimized structures. The reaction path passing through the proposed transition state (**A** → **TS** → **B**) was confirmed in terms of the intrinsic reaction coordinate (IRC) calculation.[41] All of the calculations were performed using the Gaussian 16 software package.[42] Multiwfn (Version 3.8)[43] was used for energy decomposition analysis.[44,45]

III. RESULTS AND DISCUSSION

The yield of the desired cyclized product, aza-flavanone, was found to be 88% in the presence of catalyst CBr_4 in ethanol solvent. The yield was diminished to 33% in DMSO. Only a trace amount of product was detected in benzene. When CBr_4 was absent, the product yield in ethanol decreased to 8%. The experimental findings are summarized in Table 1.

Table 1. Yield of Aza-flavanone under Different Conditions[a]



catalyst (mol %)	solvent	yield (%)[b]
CBr_4 (20)	EtOH	88
CBr_4 (20)	DMSO	33
CBr_4 (20)	C_6H_6	—
—	EtOH	8

[a]Reaction conditions: 0.179 mmol of **A** and 0.035 mmol of CBr_4 in 2.0 mL of solvent at 80 °C for 12 h. [b]Isolated yields.

The computational analysis revealed that the formation of a halogen bond between the carbonyl-O of **A** and a Br atom of CBr_4 lowers the total energy of the halogen-bonded complex **A**-CBr_4 by 21−25 kJ/mol. This translates to a bond energy of about −24 to −27 kJ/mol for the XB bond [Table 2]. In the optimized structure of **A**-CBr_4, the O−Br distance corresponding to the XB was found to be about 3.14 Å in ethanol and DMSO, and about 3.16 Å in benzene [Table 2]. These distances are shorter than the sum of the van der Waals radii of O and Br (3.350 Å) but longer than the sum of the covalent radii of O and Br (2.710 Å). This points to a bond formation. The Mulliken charges on the atoms were also found to change upon this complexation. For example, the Mulliken charge on the carbonyl-O changes from −0.32 to −0.23 in ethanol and DMSO, and from −0.27 to −0.20 in benzene [Table 3]. The

Table 2. Bond Energies[b] **of the XB in the Weakly Bound Complexes (in kJ/mol)**[a]

species	in ethanol solvent	in DMSO solvent	in benzene solvent
A-CBr_4	−23.79 (3.142)	−23.66 (3.144)	−27.32 (3.167)
TS-CBr_4	−28.13 (3.118)	−27.28 (3.031)	−35.89 (3.058)
B-CBr_4	−28.00 (2.723)	−27.70 (2.732)	−41.26 (2.986)

[a]The values in parentheses are the Br−O distances corresponding to the XB (in Å). [b]The basis set superposition error (BSSE) has been accounted for in terms of the counterpoise correction.[46]

Table 3. Mulliken Charges on O (q_O) and Br (q_{Br})

	in ethanol solvent		in DMSO solvent		in benzene solvent	
species	q_O	q_{Br}	q_O	q_{Br}	q_O	q_{Br}
A	−0.319	-	−0.322	-	−0.272	-
A-CBr_4	−0.229	0.009	−0.232	0.008	−0.204	−0.032
TS	−0.479	-	−0.482	-	−0.420	-
TS-CBr_4	−0.375	0.001	−0.365	0.003	−0.315	0.026
B	−0.590	-	−0.596	-	−0.487	-
B-CBr_4	−0.452	−0.007	−0.458	−0.008	−0.391	0.034
C	0.001	-	0.001	-	0.009	-
D	−0.358	-	−0.361	-	−0.314	-
CBr_4	-	−0.104	-	−0.104	-	−0.105

Mulliken charge on Br, the counterpart of carbonyl-O in the XB, was found to change from −0.10 to almost 0.01 in ethanol and DMSO, and to −0.03 in benzene due to the formation of the halogen-bonded complex. The plot of the electrostatic potential in ethanol in Figure 3a indicates that there is a significant electron density between carbonyl-O and Br in the complex. The change in Mulliken charges on carbonyl-O and the nearest Br atom of CBr_4 accompanied by a significant development of electron density between them also points to a bonding interaction. The plot of the relevant frontier molecular orbitals depicted in Figure 3b further affirms a weak bonding interaction between these atoms.

The reaction in Figure 2 will not take place if **A** assumes the conformation **A′** shown in Figure 4a. **A′** is stabilized through intramolecular hydrogen bonding between an amine-H and the carbonyl-O. The stabilization of **A′** relative to **A** due to intramolecular hydrogen bonding is the highest in the benzene solvent ($E_{A'} - E_A = -12.08$ kJ/mol). The lower relative stabilization of **A′** in the polar solvents (ethanol and DMSO) is likely due to its slightly lower dipole moment μ ($\mu_A = 4.25$ debye and $\mu_{A'} = 3.88$ debye in the gas phase). Moreover, the formation of intermolecular hydrogen bonds in a protic solvent (e.g., ethanol) also disrupts this intramolecular hydrogen bonding in **A′**. Therefore, it is likely that the preferred conformation of the reactant (**A**) for the reaction in Figure 2 is more abundant in ethanol than in DMSO or benzene. Figure 4b,c depicts the halogen bond formation due to CBr_4 from directions *syn* and *anti* to the aniline moiety, respectively. The approach of CBr_4 to form the XB from the direction *syn* to the aniline seems to be preferred in all solvents [Figure 3a,b]. This preference may stem from the different stereoelectronic effects ($n_O \rightarrow \sigma^*_{C-C}$) of the aniline and styrene moieties.[47] Therefore, XB formation due to CBr_4 is likely to lower the chances of intramolecular hydrogen bonding further and increase the concentration of conformer **A**.

A nucleophilic attack by the amine-N atom at the β-C atom (C atom at the β-position, with respect to the carbonyl-C, in the main chain) of **A** leads to ring closure [Figure 2]. The change in electrophilicity of the β-C atom due to the XB formation may affect this attack. The value of the Fukui function $f(\boldsymbol{r})$ at point $\boldsymbol{r}$ is

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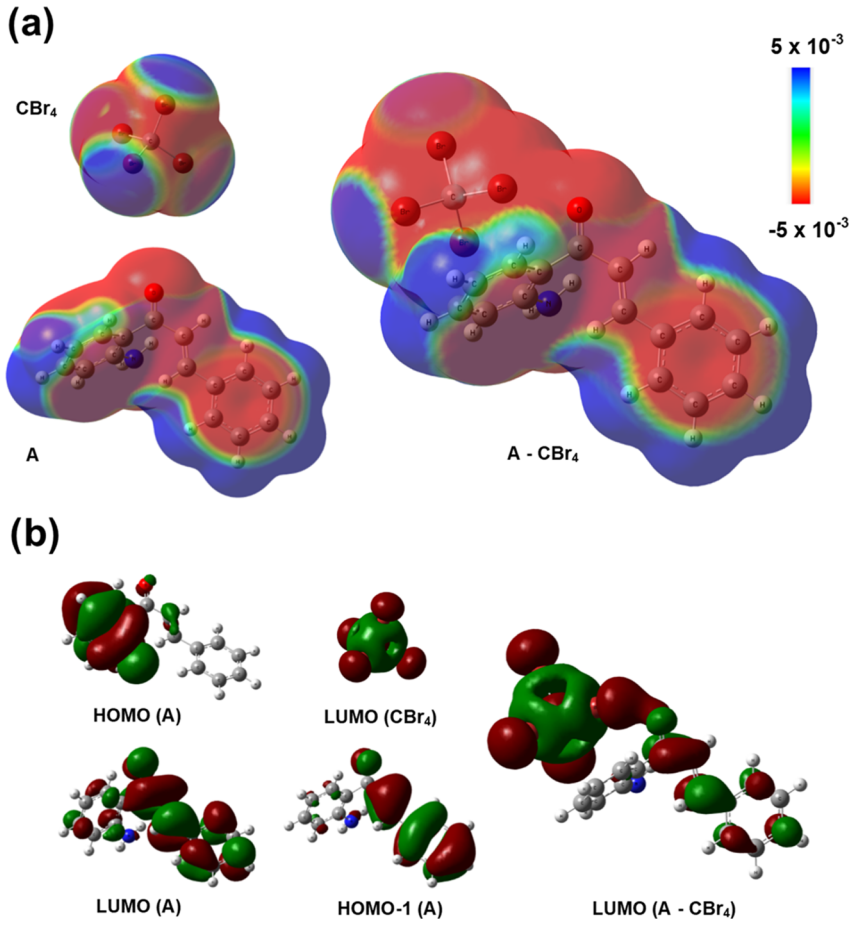
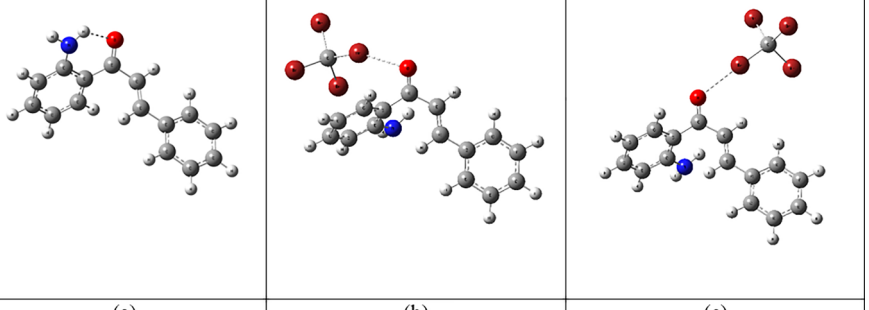


Figure 3. (a) Plots of the electrostatic potential of CBr_4, 2′-aminochalcone (**A**), and the complex of 2′-aminochalcone with CBr_4 (**A**-CBr_4). (b) The important frontier molecular orbitals of CBr_4, **A**, and **A**-CBr_4. LUMO (**A**-CBr_4) depicts the formation of the XB due to the mixing of HOMO−1 of **A** and LUMO of CBr_4.



(a)	(b)	(c)
$E_{A'} - E_A$ (kJ/mol)	$E_{A\text{-}CBr_4} - E_{CBr_4} - E_A$ (kJ/mol)	$E_{A\text{-}CBr_4} - E_{CBr_4} - E_A$ (kJ/mol)
In ethanol : −9.17 In DMSO : −8.98 In benzene : −12.08	In ethanol : −21.56 In DMSO : −21.49 In benzene : −25.26	In ethanol : −12.75 In DMSO : −12.65 In benzene : −17.44

Figure 4. Effect of intramolecular hydrogen bonding on aminochalcone (a) and the effect of halogen bonding on aminochalcone due to CBr_4 approaching from two different directions (b, c) in different solvents. E_Y refers to the total energy (sum of the electronic and zero-point energies) of Y in a given solvent. **A**′ is the preferred conformer of aminochalcone (**A**) for intramolecular hydrogen bonding between the amine-H and the carbonyl-O.

often used to characterize the nucleophilicity or electrophilicity at $\boldsymbol{r}$. It is defined as

$$f(\boldsymbol{r}) = f^{+}(\boldsymbol{r}) - f^{-}(\boldsymbol{r})$$

where

$$f^{\pm}(\boldsymbol{r}) = \pm[\rho_{N\pm1}(\boldsymbol{r}) - \rho_N(\boldsymbol{r})]$$

$\rho_N(\boldsymbol{r})$ and $\rho_{N\pm1}(\boldsymbol{r})$ are the Mulliken charges at $\boldsymbol{r}$ of the N-electron system under investigation and the corresponding $(N \pm 1)$-electron species, respectively. More negative $f(\boldsymbol{r})$ indicates a

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stronger electrophilic center at r, while more positive $f(r)$ indicates a better nucleophilic center at r.[48] The values of $f(r)$ at important atomic centers of aminochalcone in different solvents are given in Table 4. The XB formation with CBr_4 doubles the electrophilicity of the β-C center. This also seems to reduce the electrophilicity of the carbonyl-C center. In the presence of CBr_4, the nucleophilic attack by the NH_2 group at the β-C center appears to be more facile than that at the carbonyl-C. This is likely due to the ease of accommodating the incoming electron pair in the case of the former through a long conjugated framework extended until the Br atom due to the XB.

Table 4. Electrophilicity [in Terms of the Fukui Functions $f(r)$] of the Carbonyl-C and the β-C Atom of Aminochalcone (A) in Different Solvents[a]

solvents	atomic center	$f^+(r)$	$f^-(r)$	$f(r) = f^+(r) - f^-(r)$
ethanol	carbonyl-C	0.154 (0.003)	0.047 (−0.003)	0.107 (0.006)
	β - C	−0.109 (−0.151)	−0.033 (−0.003)	−0.076 (−0.148)
DMSO	carbonyl-C	0.155 (0.004)	0.049 (−0.002)	0.106 (0.006)
	β - C	−0.113 (−0.154)	−0.035 (−0.003)	−0.078 (−0.151)
benzene	carbonyl-C	0.120 (0.006)	0.010 (−0.026)	0.110 (0.032)
	β - C	−0.068 (−0.110)	−0.008 (0.013)	−0.060 (−0.123)

[a]The numbers within parentheses are the corresponding values for the aminochalcone−CBr_4 halogen-bonded complex (**A**-CBr_4).

XB interactions of CBr_4 with the species involved in the mechanistic steps of the reaction [Figure 2] are likely to affect the overall yield. For example, the formation of the XB complex between the transition state (**TS**) and CBr_4 lowers the total energy of the **TS** by 5, 4, and 9 kJ/mol in ethanol, DMSO, and benzene, respectively. A similar lowering of the total energy due to the formation of the **B**-CBr_4 complex of the zwitterion (**B**) was also observed. The corresponding changes in the bond distances and the charge densities are listed in Tables 2 and 3 [see also Tables S1 and S2 in the Supprting Information].

The activation energy barrier (E_a) is an important factor in determining the yield of the reaction within a given time. The polarity of the solvent seems to be important for E_a [see Tables 5 and 6, as well as Figure 5a]. The reaction does not seem to proceed in the nonpolar solvent benzene (dielectric constant ε = 2.2706 at 298 K). The corresponding E_a is about 129 kJ/mol (in the absence of CBr_4). The energy barrier is relatively low in the case of the polar solvents ethanol (ε = 24.852 at 298 K, E_a = 112 kJ/mol) and DMSO (ε = 46.826 at 298 K, E_a = 111 kJ/mol).

Table 5. Energy Barrier, $E_a = E_{TS} - E_{Reactant}$ (in kJ/mol), for the Reaction in Different Solvents[a]

reactant	in ethanol solvent	in DMSO solvent	in benzene solvent
A	111.87 (5.85)	110.75 (5.85)	129.15 (5.91)
A-CBr_4	106.89 (5.67)	107.08 (5.69)	120.13 (5.88)
CBr_4-**A**-EtOH	89.15 (5.64)	-	-

[a]The numbers within parentheses are the energy gap between the lowest unoccupied molecular orbital (LUMO) and the highest occupied molecular orbital (HOMO) of **A** in eV.

Table 6. Total Electronic Energy (kJ/mol) Relative to the Total Energy of Aminochalcone (A) in Ethanol of Various Species Involved in the Reaction*

reactant	in ethanol solvent	in DMSO solvent	in benzene solvent
A	0	−1.26	+19.58
A-CBr_4	−21.56	−22.75	−5.68
TS	+111.87	+109.48	+148.73
TS-CBr_4	+85.33	+84.33	+114.45
B	+87.69	+84.29	+137.00
B-CBr_4	+62.25	+59.08	+100.09
C	−10.57	−11.59	+5.83
D	−65.66	−66.74	−48.75

*The relative energy of species Y in solvent Z is calculated as $E_{Y(Z)} - E_0$ for Y = **A**, **TS**, **B**, **C**, **D** and as $E_{Y(Z)} - E_{CBr_4(Z)} - E_0$ for the halogen-bonded complexes (Y = **A**-CBr_4, **TS**-CBr_4, **B**-CBr_4), where $E_{Y(Z)}$ is the total electronic energy (sum of electronic and zero-point energies) of Y in solvent Z, $E_0 = E_{A(ethanol)} = -709.047046$ hartree, $E_{CBr_4(ethanol)} = -10335.02921$ hartree, $E_{CBr_4(DMSO)} = -10335.02927$ hartree, and $E_{CBr_4(benzene)} = -10335.02813$ hartree.

The presence of CBr_4 lowers E_a due to XB formation in all of the solvents. E_a for the reaction in ethanol and DMSO is 107 and 120 kJ/mol for that in benzene in the presence of CBr_4. However, the excellent yield of aza-flavanone in the presence of CBr_4 in ethanol (88%), in comparison to that in DMSO (33%), may owe its origin to a complex interplay among CBr_4, aminochalcone, and ethanol. It is important to notice that the protic solvent ethanol is likely to form a H-bond with the carbonyl-O. A 1:1:1 complex of these three [CBr_4-**A**-EtOH; Figure 6a] leads to a **TS** with a much lower E_a (89 kJ/mol) [Figure 6b]. We explored a number of aminochalcone structures with an explicit DMSO or benzene molecule close to carbonyl-O to see whether the resulting interactions facilitate the reaction. However, no minimum-energy structure (stationary point) in the case of DMSO or benzene molecule bound to carbonyl-O of aminochalcone could be found. We suspect that the enhancement of the reaction via explicit bonding interaction with the solvent might be absent in the case of DMSO and benzene.

The Gibbs energy of activation ($\Delta G^{\ddagger}$) for the reaction was computed from the thermochemistry calculations in Gaussian 16.[49] $\Delta G^{\ddagger}$ in ethanol in the absence of CBr_4 was found to be 121 kJ/mol. XB with CBr_4 lowers it to 119 kJ/mol. If we consider the formation of the complex CBr_4-**A**-EtOH in ethanol, then $\Delta G^{\ddagger}$ is lowered significantly to 108 kJ/mol. One can obtain the rate constants from the Eyring equation[50] $k(T) = (k_B T/h) \exp(-\Delta G^{\ddagger}/RT)$, where k_B is the Boltzmann constant, h is the Planck constant, R is the universal gas constant, and T is the experimental temperature (in Kelvins). At 80 °C, the rate constants for the above cases turn out to be 1.01×10^{-5}, 2.08×10^{-5}, and 7.84×10^{-4} s^{-1}, respectively [see Table 7]. Evidently, the presence of CBr_4 enhances the rate of the reaction in ethanol by about 2 orders of magnitude. This gives an idea about the half-life of the reactant **A** in the CBr_4-catalyzed Michael addition reaction, namely, a quarter of an hour for the reaction in ethanol (considering CBr_4-**A**-EtOH as the reactant), about 9 h in DMSO, and about 22 days in benzene. Although these are merely crude theoretical estimates, the numbers clearly point to the superior yield in ethanol within a given time frame.

The reduced energy gap between the HOMO and the LUMO of **A** in the presence of CBr_4 is a clear indication of orbital stabilization, which in turn lowers the activation energy barrier [see Table 5].[51,52] However, it was argued that lowering of the

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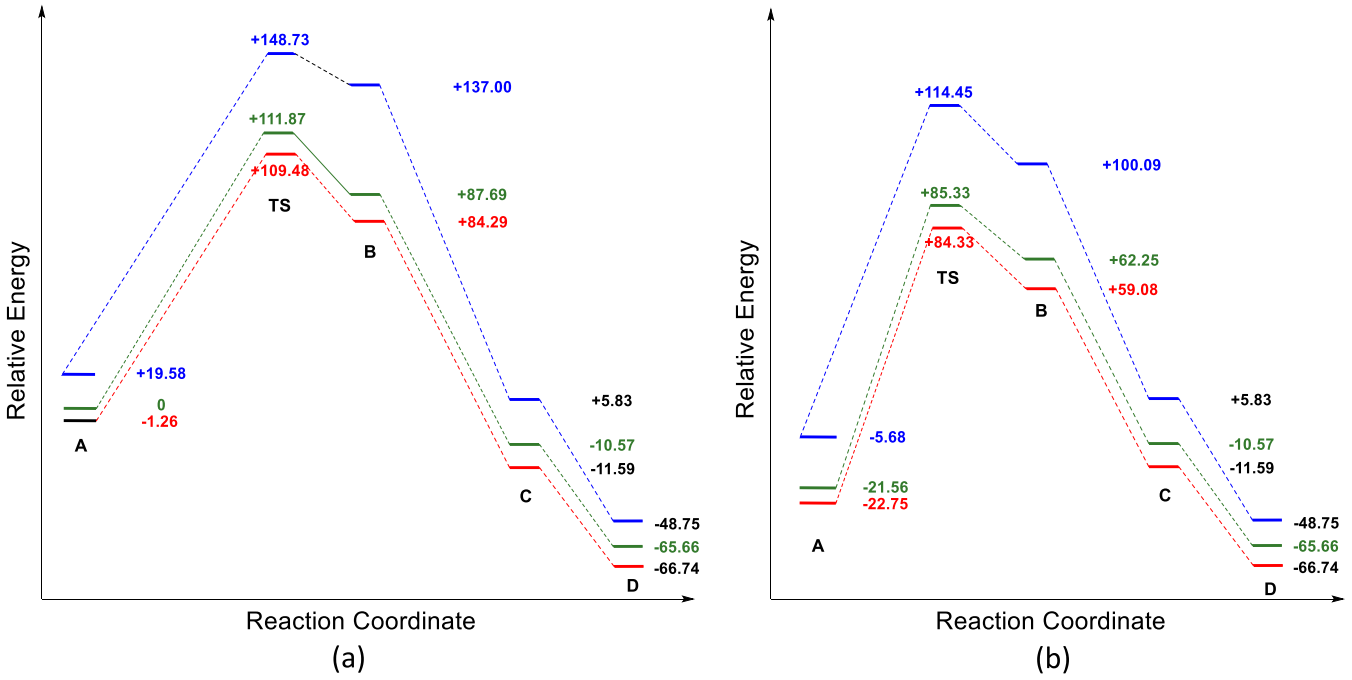

Figure 5. Energy profile diagram for the formation of aza-flavanone from aminochalcone in the absence (a) and presence (b) of CBr_4 in the solvents ethanol (green), DMSO (red), and benzene (blue). The relative energies are given in Table 6.

steric repulsion (due to the Pauli exchange interaction) may be a stronger and probably a more consistent reason for the lowering of E_a.[53−58] We undertook an energy decomposition analysis (EDA), as described by Liu[44,45] and implemented in Multiwfn software (Version 3.8),[43] to compute the steric repulsion term (E_s). For this, the results from single-point energy calculations with the B3LYP density functional[59] (as recommended by the Multiwfn software) were used. The corresponding structures were optimized earlier (Section II). In the absence of CBr_4, the relative value of the steric repulsion [E_s(**TS**) − E_s(reactant)] in ethanol on going from **A** to the **TS** was found to be −5.04 eV (reactant: **A**). This was reduced to −6.27 eV when the halogen bonding of **A** with CBr_4 was taken into account (reactant: **A**-CBr_4). However, a significant reduction in the relative steric repulsion (−10.10 eV) was observed when the hydrogen bonding with an explicit solvent molecule (ethanol) was taken into consideration in addition to the XB (reactant: CBr_4-**A**-EtOH). This further affirms that a combination of XB and H-bond formation is likely to be responsible for the excellent catalytic effect of CBr_4 in ethanol.

In addition to E_a, one should also look into the species following **TS** in the reaction pathway to rationalize the yield of the reaction. A nonpolar solvent benzene is unlikely to be effective enough in stabilizing the polar zwitterionic intermediate **B** (μ_B = 10.11 debye in the gas phase). This is evident from the fact that the formation of **B** from **TS** leads to the release of only 12 kJ/mol of energy in benzene [Figure 5a]. The energy released during the formation of **B** from the **TS** in ethanol and DMSO is approximately double that in benzene. Moreover, **B** is about 117 kJ/mol higher in energy than **A** in benzene and about 87−88 kJ/mol higher in energy than **A** in ethanol and DMSO. The low stability of **B** in benzene is likely to be an important factor behind the negligible yield of aza-flavanone. The XB interaction due to CBr_4 further lowers the energy of **B** relative to **TS** [Figure 5b]. Due to the H-bonding interactions with the solvent in addition to XB with CBr_4, the stabilization of **B** relative to **TS** is much more pronounced in ethanol [Figure 6b]. This corresponds to a release of about 32 kJ/mol energy on the formation of the zwitterionic intermediate (CBr_4-**B**-EtOH) from the transition state. CBr_4-**B**-EtOH lies about 58 kJ/mol above CBr_4-**A**-EtOH. The profound stability of the zwitterionic intermediate in ethanol in the presence of CBr_4 is likely to be an important factor behind the excellent yield of the product aza-flavanone.

IV. CONCLUSIONS

In summary, this study explored the effect of solvents on the synthesis of aza-flavanone from 2′-aminochalcone using CBr_4 as an organocatalyst via the intramolecular Michael addition. The catalytic role of CBr_4, mediated by halogen bonding (XB), significantly impacts the reaction yield (88% in ethanol, 33% in DMSO, and merely a trace amount in benzene). The reacting species were modeled computationally at the level of density functional theory (M06-2X). Grimme's D3 dispersion correction and the basis sets of triple-ζ quality were used. The effect of solvents was taken into account in terms of a polarizable continuum model based on the integral equation formalism (IEFPCM). CBr_4 was found to lower the activation energy barrier for the reaction through the reduction of the steric (Pauli) repulsion. The barrier for the reaction was found to be the highest in the case of benzene. Moreover, the low polarity of benzene might not be enough to adequately stabilize the zwitterionic intermediate that follows the transition state in the reaction pathway. The high activation barrier and the low stability of the zwitterionic intermediate may negatively affect the yield of aza-flavanone in benzene. Improved yields in ethanol and DMSO are attributed to the higher polarity of these solvents, which is likely responsible for reducing the activation barrier and stabilizing the zwitterionic intermediate. However, one needs to take into account the synergistic impact of the XB, the H-bond, and the polarity of the solvent to explain the excellent yield of aza-flavanone in ethanol.

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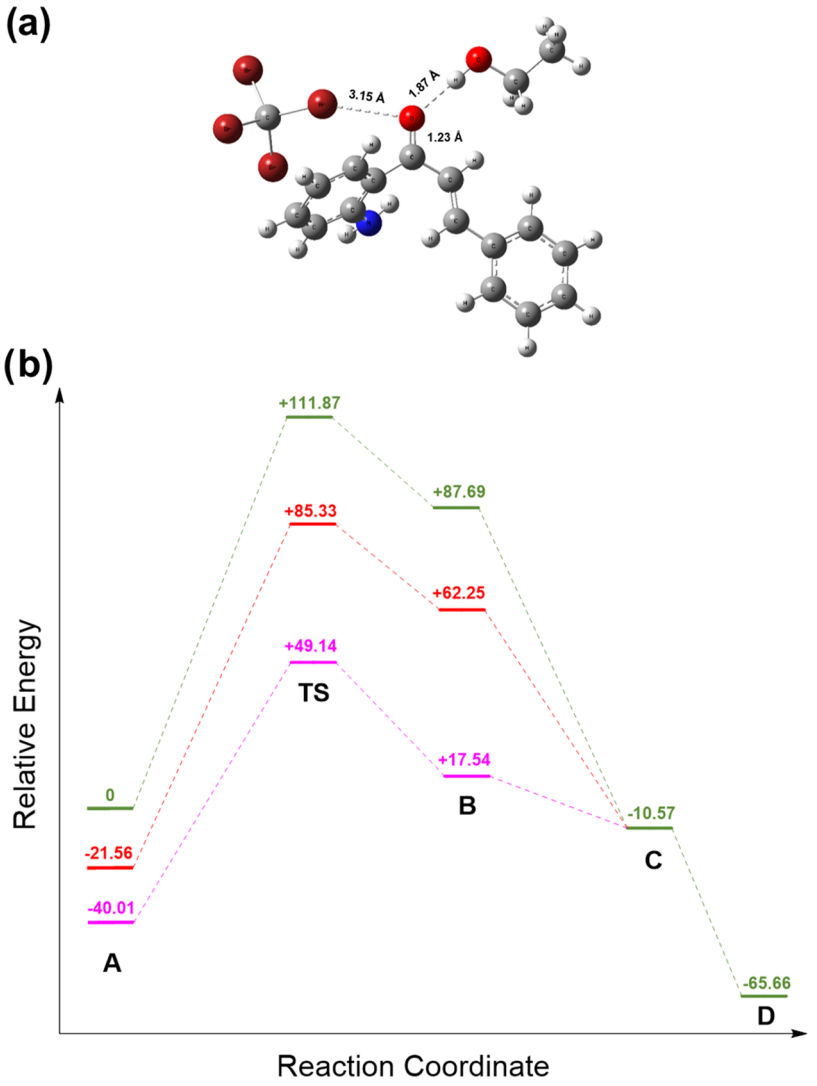

Figure 6. (a) CBr_4−aminochalcone−ethanol 1:1:1 complex (CBr_4-**A**-EtOH), (b) energy profile diagram for the formation of aza-flavanone in ethanol solvent by taking into account H-bond and XB interactions. Green: no H-bond or XB interaction was considered; red: only XB interaction with CBr_4 was considered; and purple: H-bond interaction with ethanol and XB interaction with CBr_4 was considered.

Table 7. Gibbs Energy of Activation $\Delta G^{\ddagger}$, the First-Order Rate Constant $k(T)$ at T = 353.15 K, and the Corresponding Half-Life of the Reactant ($t_{1/2}$) for the Conversion of the Reactant to the Zwitterionic Intermediate

solvents	reactant	$\Delta G^{\ddagger}$ (kJ/mol)	$k(T)$ (s^{-1})	$t_{1/2}$ (h)
EtOH	**A**	120.77	1.01×10^{-5}	1.91×10^{1}
	A-CBr_4	118.64	2.08×10^{-5}	9.27×10^{0}
	CBr_4-**A**-EtOH	107.98	7.84×10^{-4}	2.46×10^{-1}
DMSO	**A**	119.58	1.51×10^{-5}	1.28×10^{1}
	A-CBr_4	118.45	2.22×10^{-5}	8.67×10^{0}
Benzene	**A**	139.76	1.57×10^{-8}	1.23×10^{4}
	A-CBr_4	130.46	3.72×10^{-7}	5.18×10^{2}

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.3c04207.

Computational details; optimized Cartesian coordinates and energies; important bond lengths (Table S1); Mulliken Charges (Table S2); characterization data; and NMR spectra (PDF)

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Author Contributions

All of the computational investigations were done by R.R.M. under the supervision of K.S., and the experiments were done by R.B. under the supervision of P.M. The manuscript was written with the contributions from all of the authors.

Notes

The authors declare no competing financial interest.

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