Trichloroisocyanuric acid and NaNO_2 mediated nitration of indoles under acid-free and Vilsmeier–Haack conditions: synthesis and kinetic study

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Abstract

This study deals with the synthetic and kinetic aspects of trichloroisocyanuric acid (TCCA) and NaNO_2 mediated nitration of indoles in aqueous acetonitrile media under acid-free and Vilsmeier–Haack conditions (using *N,N'*-dimethyl amides) conditions. Nitration of indoles revealed second order kinetics, with a first order dependence on [indole] and [nitrating agent] ($[\text{TCCA}]/[\text{NaNO}_2]$, $[(\text{TCCA}-\text{DMF})]/[\text{NaNO}_2]$ or $[(\text{TCCA}-\text{DMA})]/[\text{NaNO}_2]$, in which $[\text{NaNO}_2]$ far excess over other reagents). Reactions followed overall second order kinetics with first order in [reagent] and [indole] under the experimental conditions. Isokinetic temperature (β) values were obtained from Leffler's equation for different kinetic protocols ($\beta = 303 \text{ K}$ (TCCA– NaNO_2); 303 K (TCCA–DMF)/ NaNO_2 ; and 244 K (TCCA–DMA)/ NaNO_2). These values are the experimental temperature range (303–323 K) indicating that the entropy factors are probably more important in controlling the reaction.

Keywords Nitration kinetics · Trichloroisocyanuric acid (TCCA) · *N,N'* dimethyl formamide (DMF) · *N,N'* dimethyl acetamide (DMA) · (TCCA–DMF) and (TCCA–DMA) adducts · Indoles · NaNO_2

1 Introduction

Indole is a bicyclic heteroaromatic molecule ($\text{C}_8\text{H}_7\text{N}$) containing a five-membered pyrrole ring fused to six-membered benzene ring. Indole is produced in nature by several bacteria; therefore, it is widely spread in the environment. It is isolated from coal tar distillate and one of the widely studied heterocyclic molecules, which regulates several aspects of bacterial physiology [1]. Tryptophan (one of the useful amino acids) is a derivative of indole, which acts as a precursor of the neurotransmitter serotonin [2]. Indole is an electron-rich heteroaromatic nitrogen heterocycle, which undergoes electrophilic substitution reactions primarily at the 3-position. Different types of nitro indole derivatives were synthesized during the past several years, which include noteworthy syntheses of Majima and Kotake [3], and Wayland Noland's research

group [4–8], and several others [9–12]. Sundberg's monograph reviewed several aspects on the chemistry of indoles [12], including electrophilic substitution reactions including nitration of indole.

Electrophilic aromatic substitution (EAS) reactions in general and aromatic nitration reactions in particular played key role in the development of organic chemistry. These leading to the synthesis of many precursors and intermediates useful for the design and execution of drugs, dyes, explosive, pharmaceuticals and several other industrially important compounds [1–11]. Eilhardt Mitscherlich was the first to prepare nitrobenzene using benzene and fuming HNO_3 in 1834 [8], followed by the use of acid mixture ($\text{HNO}_3 + \text{H}_2\text{SO}_4$) to achieve aromatic nitration. Hughes, Ingold and Reed [9] stated that Martinsen [10] was the first to accomplish definite second-order kinetics for the nitration of aromatic substances in sulphuric acid medium in

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1904, and it is believed that nitration occurs through the formation of active nitronium ion (NO_2^+) species in acid-mixture during the course of reaction [9]. Participation of the nitronium ion has been evidenced from the Raman spectroscopic studies of Kecki [11], which depicted a line at 1400 cm^{-1} in the Raman spectrum. In recent past quite a good number of workers focused their attention on quantum chemical studies to explore mechanism of nitration of aromatic compounds [12–15]. Review article published by Katrizky et al. [16] provided excellent bibliography on the direct mono nitration of wide varieties of heterocyclic compounds like furans, pyrroles, thiophenes, pyrazoles, imidazoles, isoxazoles and thiazoles using nitric acid/trifluoroacetic anhydride as nitrating agent. Adegoke et al. [17] accomplished spectrophotometric determination of metronidazole and tinidazole via charge transfer complexation using chloranilic acid. Mukherjee and Boshaff [18] explored that nitroimidazoles could be effectively used for the treatment of TB. During the past two decades our research group is also actively involved to achieve nitration using eco-friendly reagents and catalysts [19–29].

Trichloroisocyanuric acid (TCCA) was first reported by Chattaway and Wadmore [30], which has been explored as cost effective, less toxic, less corrosive, efficient, and versatile laboratory reagent for oxidation and chlorination reactions [31–33]. Recent reports from our group revealed that the TCCA/dimethyl formamide (DMF) is an efficient reagent for chloro dehydration of alcohols [34], (TCCA–DMF)/ NaNO_2 reagent for decarboxylative nitration of α , β unsaturated carboxylic acids and nitration

of aromatic compounds (under mineral acid free conditions) [35–37]. Recently, we have explored (TCCA/(DMF) and (TCCA/(DMA) as green Vilsmeier–Haack (VH) type reagents for effective synthesis of 2-chloro 3-formyl and 2-chloro 3-acetyl quinolines from acetanilides [38] respectively. Enthused by the greenery nature of TCCA, we have embarked on the synthesis and kinetic study of nitration of indole compounds mediated by trichloroisocyanuric acid/and NaNO_2 in absence and of N,N' -dimethyl amides: (i) (TCCA/ NaNO_2) and (ii) (TCCA/DMF)/ NaNO_2 and (TCCA/DMA)/ NaNO_2 under mineral acid free conditions (Scheme 1).

2 Experimental details

Chemicals used were obtained from either Avra (India) or SD-Fine Chemicals (India). Freshly prepared reagents and solutions were used for all the reactions.

2.1 Synthesis of [TCCA–DMF] and [TCCA–DMA] adducts

Trichloroisocyanuric acid/dimethyl formamide (TCCA–DMF), and (TCCA–DMA) reagents were always prepared fresh as detailed in our papers [34–36]. About 0.10 mol TCCA, and 0.13 mol of N,N' -dialkyl amides such as DMF or DMA were suspended into an RB flask containing about 50 ml of CH_2Cl_2 solvent. The contents were stirred continuously at room temperature till (for about 3 h) a

Scheme 1 Nitration of Indole compounds using TCCA and [TCCA/DAA] adduct and NaNO_2

while precipitate occurred. The resultant mass was separated as [(TCCA–DMF) (or) [TCCA–DMA)] reagent.

2.2 Method to follow the kinetics of TCCA–nitrite triggered nitration reactions

Known amounts of substrate (Indole), sodium nitrite (NaNO_2), and suitable amount of aqueous acetonitrile (MeCN) in one reaction flask (Flask-A), and trichloroisocyanuric acid (TCCA) were taken in another flask (Flask-B). Both the flasks were clamped in a thermostatic bath at a desired temperature for about 20 min. Required amount of TCCA was transferred to flask-A, mixed thoroughly to trigger the reaction. About one to two mL portions of the reaction mixture were transferred into a cuvette, placed in the thermostatic cell compartment (comprising inlet–outlet devices for the circulation of thermostatic liquid to maintain desired temperature). Absorbance (A) values of the nitro product was recorded at various time intervals (A_t) at 430 nm till 60–70% of the reaction is completed, which were reproducible with $\pm 5\%$ accuracy.

2.3 Method to follow the kinetics of nitration reactions triggered by (TCCA/DMF) and (TCCA/DMA) adducts and nitrite

Similar procedure is used to study the kinetics of nitration, when TCCA is replaced with (TCCA/DMF) and (TCCA/DMA) adducts, which were always prepared fresh every day.

2.4 Determination of the order of reaction

In the present kinetic protocols, we have defined A_t = absorbance of nitrate species produced during the course of reaction at a given time, A_∞ is the absorbance at infinite time (at the end of the reaction) and A_0 , the absorbance (if any) before the on-take of reaction, then $(A_\infty - A_t)$ is proportional to $(a - x)$ and $(A_\infty - A_0)$ proportional to (a) . To determine order of the reaction, we have used graphical method of approach based on the integrated rate expressions of second order and first order kinetics, according to standard procedures.

Under the conditions, viz., (i) $[\text{Indole}]_0 \gg [\text{TCCA}]_0$ and $[\text{NaNO}_2]_0 \gg [\text{TCCA}]_0$, (ii) $[\text{Indole}]_0 \gg [\text{TCCA–DMF}]_0$ and $[\text{NaNO}_2]_0 \gg [\text{TCCA–DMF}]_0$, (iii) $[\text{Indole}]_0 \gg [\text{TCCA–DMA}]_0$ and $[\text{NaNO}_2]_0 \gg [\text{TCCA–DMA}]_0$, the pseudo first order plots of $\ln[(A_\infty - A_0)/(A_\infty - A_t)]$ versus time were linear passing through origin with positive slope according to the following equation:

$$\ln \left[\frac{(A_\infty - A_0)}{(A_\infty - A_t)} \right] = k't \quad (1)$$

Fig. 1 Pseudo first order plot for TCCA/ NaNO_2 triggered nitration of indoles. $10^3[\text{Substrate}] = 5.0 \text{ mol/dm}^3$, $10^4[\text{TCCA}] = 5.0 \text{ mol/dm}^3$, Me-CN (% V/V) = 25, $10^2[\text{NaNO}_2] = 2.5 \text{ mol/dm}^3$

Fig. 2 Pseudo first order plot for (TCCA–DMF)/ NaNO_2 triggered nitration of indoles. $10^3[2\text{-Methyl Indole}] = 2.5 \text{ mol/dm}^3$, $10^4[\text{VHR'F}] = 2.5 \text{ mol/dm}^3$, $10^3[5\text{-Bromo Indole}] = 5.0 \text{ mol/dm}^3$, $10^4[\text{VHR'F}] = 5.0 \text{ mol/dm}^3$, $10^3[\text{Indole}] = 5.0 \text{ mol/dm}^3$, $10^4[\text{VHR'F}] = 5.0 \text{ mol/dm}^3$, Me-CN (% V/V) = 25, $10^2[\text{NaNO}_2] = 2.5 \text{ mol/dm}^3$

Fig. 3 Pseudo first order plot for (TCCA–DMA)/ NaNO_2 triggered nitration of indoles. $10^3[\text{Substrate}] = 5.0 \text{ mol/dm}^3$, $10^4[\text{VHR'A}] = 5.0 \text{ mol/dm}^3$, Me-CN (% V/V) = 25, $10^2[\text{NaNO}_2] = 2.5 \text{ mol/dm}^3$

These observations indicated first order kinetics in (i) [TCCA] (ii) [TCCA–DMF] (iii) [TCCA–DMA] in all the systems (Various Indoles) studied. Pseudo first order rate constant (k') could be obtained from the slopes of these linear plots (Figs. 1, 2, 3). First order kinetics in [Indole] was further confirmed from the observed linear plot of (k') versus [Substrate], which passed through the origin (Figs. 4, 5,

Fig. 4 Second order plots for TCCA/NaNO₂ triggered nitration of indoles. 10^4 [2-Methyl Indole] = 2.5 mol/dm³, 10^4 [TCCA] = 2.5 mol/dm³, 10^4 [5-Bromo Indole] = 5.0 mol/dm³, 10^4 [TCCA] = 5.0 mol/dm³, 10^4 [Indole] = 5.0 mol/dm³, 10^4 [TCCA] = 5.0 mol/dm³, Me-CN (% V/V) = 25, 10^2 [NaNO₂] = 2.5 mol/dm³. Temp = #03 K

Fig. 5 Second order plots for (TCCA-DMF)/NaNO₂ triggered nitration of indoles. 10^4 [2-Methyl Indole] = 2.5 mol/dm³, 10^4 [VHR'F] = 2.5 mol/dm³, 10^4 [5-Bromo Indole] = 5.0 mol/dm³, 10^4 [VHR'F] = 5.0 mol/dm³, 10^4 [Indole] = 5.0 mol/dm³, 10^4 [VHR'F] = 5.0 mol/dm³, Me-CN (% V/V) = 25, 10^2 [NaNO₂] = 2.5 mol/dm³. Temp = 323 K

Fig. 6 Second order plots for (TCCA-DMA)/NaNO₂ triggered nitration of indoles. 10^4 [Substrate] = 5.0 mol/dm³, 10^4 [VHR'A] = 5.0 mol/dm³, Me-CN (% V/V) = 25, 10^2 [NaNO₂] = 2.5 mol/dm³. Temp = 323 K

6). When (i) TCCA, (ii) [TCCA-DMF], (iii) [TCCA-DMA] and [Substrate] (i.e., Indole) are taken in equal concentrations (i.e., (i) [TCCA]₀ = [Indole]₀), [NaNO₂]₀ >> [TCCA]₀ (ii)

Fig. 7 Plots of (k') versus [Sub] in TCCA/NaNO₂ triggered nitration reactions of indoles at 313 K

Fig. 8 Plots of (k') versus [Sub] in TCCA/NaNO₂ triggered nitration reactions of indoles at 313 K

[TCCA-DMF]₀ = [Indole]₀, [NaNO₂]₀ >> [TCCA-DMF]₀ (iii) [TCCA-DMA]₀ = [Indole]₀, and [NaNO₂]₀ >> [TCCA-DMA]₀ plots of $1/(A_{\infty} - A_t)$ versus time, have been found to be linear with a positive gradient and definite intercept on vertical axis indicating over all second order kinetics (Figs. 7, 8, 9), according to the following expression:

$$\frac{1}{(A_{\infty} - A_t)} = \frac{k}{(\varepsilon)}(t) + \frac{1}{(A_{\infty} - A_0)} \quad (2)$$

(Where $\varepsilon = [\text{Reagent}]_0 / (A_{\infty} - A_0)$)

Fig. 9 Plots of (k') versus [Sub] in (TCCA–DMF)/ NaNO_2 triggered nitration reactions of indoles at 313 K

Proper substitution of (ϵ) into the above equation leads to

$$\frac{1}{(A_\infty - A_t)} = \frac{k[\text{Reagent}]_0}{(A_\infty - A_0)}(t) + \frac{1}{(A_\infty - A_0)} \quad (3)$$

Kinetic features, observed in Trichloroisocyanuric acid (TCCA) triggered nitration of indoles under acid free and Vilsmeier–Haack conditions, when $[\text{NaNO}_2] \gg [\text{Other reactants}]$ are compiled in Table 1.

2.5 Effect of added olefinic monomer to determine the participation of free radicals

We have tried to gain insight participation of free radicals using olefinic monomers (acrylamide and acrylonitrile) as additives in the reaction mixture. For this purpose, we have added freshly prepared and deaerated acrylamide or deaerated acrylonitrile to the reaction mixture containing TCCA, NaNO_2 , Indole under inert (nitrogen) atmosphere. Participation of free radicals is generally indicated by the formation of dense polyacrylamide (or viscous poly acrylonitrile if acrylonitrile is used as monomer). If free radicals are generated in situ in the reaction, the generated free

radicals induce the formation of olefinic monomer radical (acrylamide and acrylonitrile radical), which in turn propagate the reaction and finally polymer is formed. But added olefinic monomers did not undergo polymerization even after 24 h, suggesting that free radicals are not formed in the present study.

2.6 Product analysis under kinetic conditions

After ensuring completion of the reaction kinetics, the reaction mixture is washed with aqueous NaHCO_3 and ethylacetate. Organic layer was separated, dried over MgSO_4 . This product was further purified over column chromatography using ethylacetate: hexane as eluent. Isolated yields of products of nitration under acid free and Vilsmeier–Haack conditions are compiled in Table 2.

- 3-nitroindole: Pale yellow solid, Melting Point: 215–218 °C. ^1H NMR (CDCl_3 , 500 MHz) δ 11.86 (s, 1H), 8.72 (s, 1H), 8.05–8.09 (m, 1H), 7.58–7.61 (m, 1H), 7.31–7.38 (m, 2H). ^{13}C NMR (126 MHz, $\text{DMSO}-d_6$) δ : 142.2, 141.5, 128.9, 126.6, 122.7, 120.8, 119.8, 111.8. EI-MS m/z^{-1} (%): 162.04 (M^+) (100). Anal.Data: Calcd. for $\text{C}_8\text{H}_6\text{N}_2\text{O}_2$ (in %): C-59.26; H-3.73; N-17.28. Found: C-59.19; H-3.51; N-17.02.
- 2-methyl-5-nitroindole: Yellow solid, Melting Point: 311–314 °C. ^1H NMR (CDCl_3 , 500 MHz): δ 10.1 (s, 1H), 8.91 (s, 1H), 8.52 (s, 1H), 8.16 (d, $J=8.9$ Hz, 1H), 7.72 (d, $J=8.6$ Hz, 1H). ^{13}C NMR (126 MHz, $\text{DMSO}-d_6$) δ : 185.6, 143.9, 138.6, 131.2, 127.8, 125.9, 118.7, 114.5, 112.3. EI-MS m/z^{-1} (%): 190.04 (M^+) (100). Anal.Data: Calcd. for $\text{C}_9\text{H}_6\text{N}_2\text{O}_3$ (in %): C-56.85; H-3.18; N-14.73. Found: C-56.58; H-3.09; N-14.59.
- 5-bromo-3-nitroindole: Brown solid, Melting Point: 285–288 °C. ^1H NMR (CDCl_3 , 500 MHz, CDCl_3) δ 10.09 (s, 1H), 8.29 (s, 1H), 7.78 (s, 1H), 7.41 (d, $J=2.9$ Hz, 1H). ^{13}C NMR (126 MHz, $\text{DMSO}-d_6$) δ : 141.9, 139.6, 126.4,

Table 1 Kinetic observations in trichloroisocyanuric acid (TCCA) mediated nitration of Indoles under acid free and Vilsmeier–Haack conditions

Kinetic plots	Reagent/system	Figures	Result
First order in [TCCA reagent]: the $\ln[(A_\infty - A_0)/(A_\infty - A_t)]$ versus time plots were linear	Order in [TCCA]	Figure 1	One
	Order in [TCCA/DMF]	Figure 2	One
	Order in [TCCA/DMA]	Figure 3	One
Plots of $1/(A_\infty - A_t)$ versus time plots were linear with positive slope and intercept as shown in Figs. 4, 5 and 6	TCCA system	Figure 4	Plots here in show over all second order kinetics
	[TCCA/DMF] system	Figure 5	
	[TCCA/DMA] system	Figure 6	
First order in [substrate]: Plots of (k') versus [substrate] were liner with positive slope	TCCA system	Figures 7 and 8	One
	[TCCA/DMF] system	Figures 9 and 10	One
	[TCCA/DMA] system	Figures 11 and 12	One

125.5, 124.2, 121.6, 114.8, 113.5. EI-MS m/z^{-1} (%): 239.95 (M^+) (100). Anal.Data: Calcd. for $C_8H_5BrN_2O_2$ (in %): C-39.86; H-2.09; N-11.62. Found: C-39.58; H-2.25; N-11.51.

- (d) 5-Nitro-3-indolecarbaldehyde: Yellow solid, Melting Point: 311–314 °C. ^1H NMR ($CDCl_3$, 500 MHz): δ 10.1 (s, 1H), 8.91 (s, 1H), 8.52 (s, 1H), 8.16 (d, $J=8.9$ Hz, 1H), 7.72 (d, $J=8.6$ Hz, 1H). ^{13}C NMR (126 MHz, $DMSO-d_6$) δ : 185.6, 143.9, 138.6, 131.2, 127.8, 125.9, 118.7, 114.5, 112.3. EI-MS m/z^{-1} (%): 190.04 (M^+) (100). Anal.Data: Calcd. for $C_9H_6N_2O_3$ (in %): C-56.85; H-3.18; N-14.73. Found: C-56.58; H-3.09; N-14.59.
- (e) 5-Nitro-3-indoleacetic acid: Solid, Melting Point: 215–218 °C. ^1H NMR ($CDCl_3$, 500 MHz) δ 10.07 (s, 1H), 8.36–8.28 (m, 1H), 7.86 (d, $J=3.0$ Hz, 1H), 7.48–7.41 (m, 1H), 7.36–7.31 (m, 2H). ^{13}C NMR (126 MHz, $DMSO-d_6$) δ : 174.8, 143.3, 132.8, 128.9, 127.1, 123.3, 114.7, 112.2, 107.6, 31.8. EI-MS m/z^{-1} (%): 220.05 (M^+) (100). Anal.Data: Calcd. for $C_{10}H_8N_2O_4$ (in %): C-54.55; H-3.66; N-12.72. Found: C-54.62; H-3.28; N-12.51.
- (f) 5-Nitro-3-indolethylamine: Solid, Melting Point: 215–218 °C. ^1H NMR ($CDCl_3$, 500 MHz, $CDCl_3$) δ 10.07 (s, 1H), 8.36–8.28 (m, 1H), 7.86 (d, $J=3.0$ Hz, 1H), 7.48–7.41 (m, 1H), 7.36–7.31 (m, 1H). ^{13}C NMR (126 MHz, $DMSO-d_6$) δ : 174.8, 143.3, 132.8, 128.9, 127.1, 123.3, 114.7, 112.2, 107.6, 31.8. EI-MS m/z^{-1} (%): 205.09 (M^+) (100). Anal.Data: Calcd. for $C_{10}H_{11}N_3O_2$ (in %): C-58.53; H-5.40; N-20.48. Found: C-58.21; H-5.39; N-20.13.

3 Results and discussion

3.1 Kinetics and mechanism of the TCCA/ $NaNO_2$ triggered nitration reaction

The structure of indole shows that it is a bicyclic heteroaromatic compound (C_8H_7N) containing a five-membered pyrrole ring fused to six-membered benzene ring.

Fig. 10 Plots of (k') versus [Sub] in (TCCA-DMF)/ $NaNO_2$ triggered nitration reactions of indoles at 313 K

Fig. 11 Plots of (k') versus [Sub] in (TCCA-DMA)/ $NaNO_2$ triggered nitration reactions of indoles at 313 K

Pyrrole ring is the most reactive portion of indole, and electrophilic substitution occurs preferably at C-3. Substitution of the carbocyclic (benzene) ring can be expected only after N-1, C-2, and C-3 of indole are substituted [39]. But, electrophilic attack of indoles in position 3 is in accord with the fact that this is the carbon atom with the highest electron density [40–42]. During the synthesis of Indole-3-aldehyde, James and Snyder observed that the most reactive position on indole for electrophilic aromatic substitution is C-3, which is 10^{13} times more reactive than benzene [43]. However, a noteworthy exception took place when Noland, Smith, and Rush, carried out nitration of 2-Phenylindole under acidic conditions [44–52]. Electrophilic nitration took place at C-5 (carbocyclic ring), because C-3 of pyrrole ring is protonated. This aspect

Fig. 12 Plots of (k') versus [Sub] in (TCCA-DMA)/ $NaNO_2$ triggered nitration reactions of indoles at 313 K

Table 2 Isolated yields of products in trichloroisocyanuric acid (TCCA) triggered nitration of Indoles under acid free and Vilsmeier–Haack conditions

Indoles	Reagent	Product	Yield (%)	M.P (°C)
2-Methyl indole	TCCA	2-Methyl-5-nitroindole	79 73 75	172–175
	(TCCA–DMF) adduct (TCCA–DMA) adduct			
5-Bromo indole	TCCA	5-Bromo-3-nitroindole	80 70 81	285–288
	(TCCA–DMF) adduct (TCCA–DMA) adduct			
Indole	TCCA	3-Nitroindole	86 80 83	215–218
	(TCCA + DMF) adduct (TCCA + DMA) adduct			
Indole-3-Acetic acid	TCCA	5-Nitroindole-3-acetic acid	79 79 75	289–291
	(TCCA + DMF) adduct (TCCA + DMA) adduct			
Indole-3-carbaldehyde	TCCA	5-Nitroindole-3-carbaldehyde	82 79 81	311–314
	(TCCA + DMF) adduct (TCCA + DMA) adduct			
Indole-3-ethylamine	TCCA	5-Nitroindole-3-ethylamine	69 81 73	198–201
	(TCCA + DMF) adduct (TCCA + DMA) adduct			

could also be seen from the work of Da Settimo and Saetone [53], which carried out nitration of some methyl substituted indole-3-aldehydes in sulphuric acid medium. The nitration of 1-methylindole-3-aldehyde, 2-methylindole-3-aldehyde and 1, 2-dimethylindole-3-aldehyde in sulphuric acid afforded mixtures of the corresponding C-5, and C-6-nitro derivatives, containing little excess of the 5-nitro derivatives. This aspect could also be seen from another work of Sundberg [38] on nitration of methyl derivatives of indole-3-aldehyde in binary mixtures of nitric and acetic acids. In this investigation they observed that 2-Methyl indole-3-aldehyde gave 6-nitro derivative, together with some 2-methyl-3-nitro- and 2-methyl-3, 6-dinitroindole.

On the other hand, several research groups successfully used trichloroisocyanuric acid (TCCA) as effective green oxidizing and chlorinating agent because it is non-toxic, inexpensive and easily available. Earlier reviews and publications on the chemistry of TCCA [31–33] suggested that TCCA instantaneously hydrolyses to give hypochlorous acid (HOCl). In an earlier publication Lahoutifard research group [54] efficiently

oxidizes nitrite ion in aqueous solutions. In a recent publication we have reported that nitration of aromatic compounds can be easily achieved using TCCA/NaNO₂. On the basis of earlier reports [31–33, 54] and the results of our earlier work [36] we have explained mechanism of the reaction that the HOCl released due to the hydrolysis of TCCA reacts immediately with NaNO₂ (which is large excess compared to TCCA) and liberates active nitronium ion electrophile (NO₂⁺). This contention can be supported on the findings of Margerum et al. [55] and Wahman et al. [56]. In these publications they have suggested that the formation of reactive nitryl chloride (NO₂Cl) intermediate occurs due to the reaction between nitrite and HOCl. Nitryl chloride (NO₂Cl) thus formed may generate Nitronium ion (NO₂⁺) in situ, which may convert indole into nitro indole. Observed spectroscopic and physical data revealed that nitration of parent indole underwent mono nitration at C-3 to afford 3-nitroindole as explained earlier. However, when C-3 is blocked nitration occurred at C-5 while C-5 is protected nitration occurred at C-3, which could be

Scheme 2 TCCA/ NaNO_2 triggered nitration of indoles

seen from the spectroscopic and physical data given in Table 2. At the same time, 2-Methyl indole underwent mononitration at C-5 and afforded 2-methyl-5-nitroindole, by preventing nitration at C-3. This observation could be probably attributed to the steric hindrance arising from bulky methyl group present at C-2 position which prevented nitration at neighbouring C-3 position. On the basis of foregoing discussions, a most plausible mechanism could be proposed as shown in Scheme 2.

3.2 Kinetics and mechanism of the (TCCA–DMF)/ NaNO_2 and (TCCA–DMA)/ NaNO_2 triggered nitration

In this part of the present study the isolated [TCCA–DMF], and [TCCA–DMA] adducts were used in presence of large excess of NaNO_2 to achieve nitration of indoles. The observed kinetic features (compiled in Table 1 of the present study) are almost similar to those given in our earlier work [57]. The isolated [TCCA–DMF], and [TCCA–DMA] adducts together with the IR and NMR spectroscopic observations pertaining to TCCA, *N,N'*-dialkyl amides (DAA: DMF and DMA) recorded in our earlier publications [34–36] further lend support that a similar mechanism could be operative in the nitration of indoles also. Basically, interaction of *N,N'*-dialkyl amides (DAA: DMF and DMA) with TCCA suggests the formation of Vilsmeier–Haack type intermediate species (chloromethyleniminium cation: $[(\text{CH}_3)_2\text{N}=\text{C}(\text{R})\text{Cl}]^+$). But in the presence of excess NaNO_2 , chloromethyleniminium cation species reacts with NaNO_2 to generate nitro methyleniminium cation: $[(\text{CH}_3)_2\text{N}=\text{C}(\text{R})(\text{NO}_2)]^+$ species, which is similar to Vilsmeier–Haack type

species with nitro (NO_2) group. Nitro methyleniminium cation species ($[(\text{CH}_3)_2\text{N}=\text{C}(\text{R})(\text{NO}_2)]^+$) produced in this step then reacts with indole in the slow step to afford corresponding nitro indole as detailed in Scheme 3.

3.3 Temperature effect and computation of activation parameters

From the mechanistic schemes 2 and 3, nitration reactions under different conditions are in accordance with second order rate law under conditions ($[\text{NaNO}_2]_0 \gg [\text{Nitronium ion source}]_0$ (where $[\text{Nitronium ion source}]_0 =$ (i) $[\text{TCCA}]_0$ (ii) $[\text{TCCA–DMF}]_0$ (iii) $[\text{TCCA–DMA}]_0$).

$$\frac{d[P]}{dt} = k[\text{Nitronium ion source}][\text{Indole}] \quad (4)$$

Here, $[\text{Nitronium ion source}]_0 =$ (i) $[\text{TCCA}]_0$ (ii) $[\text{TCCA–DMF}]_0$, or (iii) $[\text{TCCA–DMA}]_0$ depending on the reaction system. Therefore, above equation can be written as,

$$\frac{d[P]}{dt} = k[\text{TCCA Reagent}][\text{Indole}] \quad (5)$$

where $[\text{TCCA Reagent}]_0 =$ (i) $[\text{TCCA}]_0$ (ii) $[\text{TCCA–DMF}]_0$, or (iii) $[\text{TCCA–DMA}]_0$ because nitronium ion (NO_2^+) electrophile herein is generated in situ under the conditions ($[\text{NaNO}_2]_0 \gg [\text{TCCA Reagent}]_0$. Second order rate constants (k) were determined at different temperatures, which increased with temperature as suggested by Arrhenius theory of temperature effect [on reaction rates (Tables 3, 4). Eyring's theory of reaction rates [59, 60] is used for the computation of free energy of activation ($\Delta G^\ddagger$) at any specific temperature (T),

Scheme 3 Nitration of Indoles triggered by NaNO₂/Vilsmeier–Haack type adducts ([TCCA–DMF] or [TCCA–DMA])

$$k = (k_t)(RT/Nh)\exp(-\Delta G^\ddagger/RT) \quad (6)$$

where the transmission coefficient (k_t) is generally equal to unity. Taking natural logarithms of Eq. (6), ($\Delta G^\ddagger$) equation could be rearranged as,

$$\Delta G^\ddagger = RT \ln(RT/Nh k) \quad (7)$$

Substitution of proper values of R, N, and h values (SI units) into Eq. (7), $\Delta G^\ddagger$ could be again simplified to Eq. (8),

$$\Delta G^\ddagger = 8.314 \times T [23.7641 + \ln(T/k)] \quad (8)$$

Second order rate constants (k) and computed ($\Delta G^\ddagger$) values at various temperatures are compiled in Table 3. At this stage enthalpy and entropies of activation ($\Delta H^\ddagger$ and $\Delta S^\ddagger$) values could be obtained from the Gibbs–Helmholtz plot of ($\Delta G^\ddagger$) versus temperature (T) according to Eq. (9).

$$\Delta G^\ddagger = \Delta H^\ddagger - T\Delta S^\ddagger \quad (9)$$

Accordingly, the plot of ($\Delta G^\ddagger$) versus (T) should give a straight line with negative slope ($\Delta S^\ddagger$) and intercept ($\Delta H^\ddagger$) on ordinate. But in practice, either positive or negative slope may be obtained depending on the nature of the transition state (Figs. 13, 14, 15). If the slope is negative, magnitude of entropy of activation ($\Delta S^\ddagger$) is positive and vice versa. Positive ($\Delta S^\ddagger$) shows a dissociative mechanism, and a non-rigid or loosely bound transition state in which reactant molecules move randomly by making it unstable. On the contrary, negative magnitude of ($\Delta S^\ddagger$) generally suggests greater solvation of the transition state, followed

by an associative mechanism in which two reaction partners form a single activated complex [61]. Obtained enthalpy of activation ($\Delta H^\ddagger$), and entropy of activation ($\Delta S^\ddagger$) values are compiled in Table 4.

3.3.1 Enthalpy ($\Delta H^\ddagger$) and entropy of activation ($\Delta S^\ddagger$) relationship and compensation effect

A closer insight into the data presented in Table 4 revealed that the enthalpy ($\Delta H^\ddagger$) and entropy of activation ($\Delta S^\ddagger$) the reactions are neither isentropic (iso entropic) nor isenthalpic (iso enthalpic) but represent compensation effect of both ($\Delta H^\ddagger$) and ($\Delta S^\ddagger$), as suggested by Shorter and Hinshelwood [62–66]. According to their classification, isenthalpic (iso-enthalpic) reactions do not show any variation in ($\Delta H^\ddagger$) values with the structural variation of substituent and the reactions are completely controlled by entropy of action ($\Delta S^\ddagger$) values. Contrary to this in isentropic (iso entropic) reactions structural variation of substituent do not show any variation in the entropy of action ($\Delta S^\ddagger$) values and the reactions are controlled by enthalpy of activation (ΔH). In the last category, structural variation of substituent has significant effect on both ($\Delta H^\ddagger$) and ($\Delta S^\ddagger$) factors. The ($\Delta H^\ddagger$) values are paralleled by and ($\Delta S^\ddagger$) factors, in such way that the reactions could be either enthalpy ($\Delta H^\ddagger$) controlled or entropy ($\Delta S^\ddagger$) controlled. To understand further and interpret these reactions, Leffler [67, 68] introduced the concept of isokinetic temperature (β) in chemical kinetics (and isoequilibrium temperature (β) in chemical equilibria), and suggested an equation to calculate (β):

$$\Delta H^\ddagger = \beta \Delta S^\ddagger + \Delta H_0^\ddagger$$

Table 3 Second order rate constant (k) and free energy of activation ($\Delta G^\ddagger$) values

Substrate	Temp (K)	(k) dm ³ /mol.min			($\Delta G^\ddagger$) kJ/mol		
		TCCA	(TCCA + DMF)	(TCCA + DMA)	TCCA	(TCCA + DMF)	(TCCA + DMA)
2-Methyl indole	303	1.36	1.12	3.92	73.5	73.9	70.8
	308	2.56	1.68	5.16	73.1	74.2	71.3
	313	4.72	2.52	6.76	72.7	74.4	71.8
	318	8.40	3.72	8.84	72.4	74.6	72.3
	323	14.84	5.44	11.36	72.1	74.8	72.8
5-Bromo indole	303	0.74	0.46	0.70	75.0	76.2	75.1
	308	0.96	0.60	0.92	75.6	76.8	75.7
	313	1.22	0.80	1.20	76.3	77.4	76.3
	318	1.54	1.04	1.54	76.9	77.9	76.9
	323	1.92	1.32	2.02	77.6	78.6	77.4
Indole	303	2.80	1.20	0.90	71.6	73.8	74.5
	308	3.04	1.44	1.18	72.7	74.6	75.1
	313	3.44	1.80	1.58	73.6	75.2	75.6
	318	3.92	2.12	2.10	74.4	76.1	76.1
	323	4.22	2.50	2.74	75.5	76.8	76.6
Indole-3-acetic acid	303	0.48	0.50	0.52	76.1	75.9	75.9
	308	0.60	0.62	0.66	76.8	76.7	76.6
	313	0.74	0.78	0.80	77.6	77.4	77.4
	318	0.90	0.94	0.96	78.3	78.2	78.1
	323	1.10	1.20	1.16	79.1	78.8	78.9
Indole-3-carboxaldehyde	303	1.12	1.36	1.80	73.9	73.5	72.8
	308	1.48	1.64	2.24	74.5	74.2	73.4
	313	1.84	2.04	2.84	75.2	74.9	74.1
	318	2.36	2.56	3.64	75.8	75.6	74.6
	323	2.96	2.92	4.64	76.4	76.4	75.2
Indole-3-ethylamine	303	1.36	1.20	1.48	73.5	73.8	73.2
	308	1.80	1.44	1.92	74.0	74.6	73.8
	313	2.40	1.76	2.36	74.5	75.3	74.5
	318	3.08	2.12	3.00	75.1	76.1	75.1
	323	3.92	2.56	3.76	75.6	76.8	75.7

Table 4 Activation parameters ($\Delta H^\ddagger$ and $\Delta S^\ddagger$) using TCCA and TCCA Adducts

Activation parameter	Substrate	TCCA	(TCCA + DMF) adduct	(TCCA + DMA) adduct
$\Delta H^\ddagger$ (kJ/mol)	2-Methyl indole	94.5	61.8	40.8
	5-Bromo indole	36.1	40.7	40.3
	Indole	14.9	27.6	43.0
	Ind-3-acetic acid	31.0	32.7	29.6
	Ind-3-carboxaldehyde	36.6	29.5	36.155
	Ind-3-ethylamine	40.6	28.4	35.0
$-\Delta S^\ddagger$ (J/K/mol)	2-Methyl indole	-69.6	40.2	99.0
	5-Bromo indole	128	117	115
	Indole	187	152	104
	Ind-3-acetic acid	148	143	155
	Ind-3-carboxaldehyde	123	145	121
	Ind-3-ethylamine	108	150	126

Fig. 13 Gibbs-Helmholtz plot ($\Delta G^\ddagger$ vs. T) for TCCA/ NaNO_2 triggered nitration of indoles

Fig. 14 Gibbs-Helmholtz plot ($\Delta G^\ddagger$ vs. T) for (TCCA-DMF)/ NaNO_2 triggered nitration of indoles

Fig. 15 Gibbs-Helmholtz plot ($\Delta G^\ddagger$ vs. T) for (TCCA-DMA)/ NaNO_2 triggered nitration of indoles

where $\Delta H_0^\ddagger$ is constant irrespective of the nature of substituents. Further, it was also stated that at isokinetic temperature (β), all the compounds in the reaction series occur with the same reaction rate. The variation of substituent does not alter the rate constant and corresponding free energy of activation ($\Delta G^\ddagger$). chemical reaction. However, in isentropic (or iso entropic) reactions, isokinetic temperature (β) value is very high (as high as it would be infinity) and the reactions are controlled by enthalpy of activation,

Fig. 16 Leffler's Plot of $\Delta H^\ddagger$ versus $\Delta S^\ddagger$ for TCCA-Indoles reactions

Fig. 17 Leffler's Plot of $\Delta H^\ddagger$ versus $\Delta S^\ddagger$ for (TCCA-DMF)-Indoles reactions

Fig. 18 Leffler's Plot of $\Delta H^\ddagger$ versus $\Delta S^\ddagger$ for (TCCA-DMA)-Indoles reactions

while the isokinetic temperature (β) is zero for an isenthalpic (iso-enthalpic) series, and the reactivity is determined by the entropy of activation. In the present work the Leffler plots of ($\Delta H^\ddagger$) versus ($\Delta S^\ddagger$) were found to be linear with very high (R^2) values as shown in Figs. 16, 17 and 18.

The isokinetic temperature (β) values for the studied nitration protocols are shown below:

Reagent	β (K)
TCCA/ NaNO_2	303
(TCCA + DMF) adduct/ NaNO_2	303
(TCCA + DMA) adduct/ NaNO_2	244

The isokinetic temperature (β) values presented for (TCC/ NaNO_2) and [(TCCA + DMF) Adduct/ NaNO_2] mediated nitration reactions (303 K for both the systems) are

very close to the experimental temperature range (303 K to 323 K), while the (β) value for [(TCCA + DMA) Adduct/ NaNO_2] mediated nitration reactions (244 K) is far below the experimental temperature. The observed isokinetic temperature (β) values most probably suggest that the reactions are controlled by entropy factors as suggested by earlier literature reports. At this point it is worth mentioning that Leffler's approach for the determination of isokinetic temperature (β) is criticized by some research groups [69, 70], yet the theory is used by several other research groups [71–74].

3.4 Conclusions

In the present work we have developed trichloroisocyanuric acid (TCCA)/ NaNO_2 , (TCCA–DMF)/ NaNO_2 and (TCCA–DMA)/ NaNO_2 mediated nitration of indoles by keeping [NaNO_2] large excess over other [reactants] under acid free conditions. The reaction followed second order kinetics with first order dependence on [Nitrating agent] and [Indole]. A closer look into the obtained kinetic data revealed that the reaction is sensitive to the structural variation of indole. Nitration of parent indole took place at C-3 position of parent indole and gave 3-nitroindole. But, when C-3 is protected nitration underwent at C-5, when C-5 is protected nitration took place at C-3. At the same time, 2-Methyl indole underwent mononitration at C-5 and afforded 2-methyl-5-nitroindole, by preventing nitration at C-3. This observation could be probably attributed to the steric hindrance arising from bulky methyl group present at C-2 position which prevented nitration at neighbouring C-3 position.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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