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Unveiling the Mechanism of *N*-Methylation of Indole with Dimethylcarbonate Using either DABCO or DBU as Catalyst

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ABSTRACT

Depending on the catalyst used, *N*-methylation of indole with dimethylcarbonate (DMC) - an environmentally friendly alkylation agent – yields different products. With 1,4-diazabicyclo[2.2.2]octane (DABCO), the reaction forms only *N*-methylated indole but with or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), both *N*-methylated and *N*-methoxycarbonylated indole are formed. Using direct ESI(+)-MS monitoring to collect actual snapshots of the changing ionic composition of the reaction solution, we report on the interception and characterization of key intermediates for such reactions. Although a mechanism has been proposed with methoxycarbonylated base as the key intermediate for both DBU and DABCO, the ESI(+)-MS data as well as B3LYP-D3/6-311+G** calculations suggest that the reaction of DMC with indole under either DABCO or DBU catalysis follow contrasting mechanisms.

Keywords:

Introduction

Indole is commonly found in nature as part of the structural backbone of many natural products. This heterocyclic motif functions also as a fundamental organic subunit in synthetic chemistry, normally imparting powerful and diverse bioactivity to drugs.[1-4] *N*-methylation of indoles is also an important step in organic synthesis since this is the most common form of indole found in nature, such as in indole alkaloids, which exhibit various biological[5] and pharmacological activities (**Figure 1**).[2]
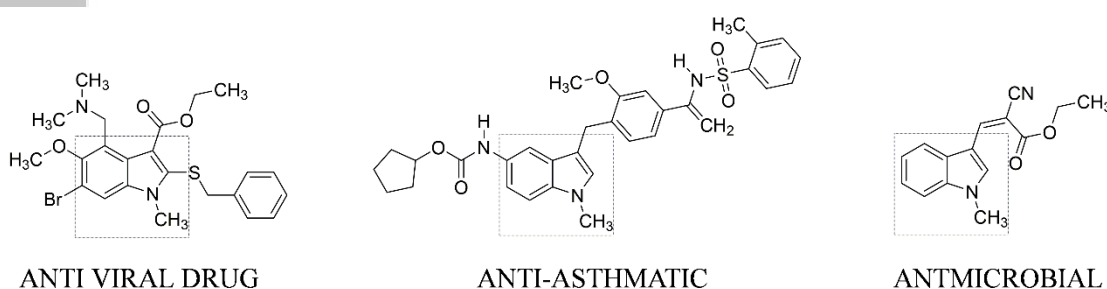
Figure 1. Key *N*-methylated indole subunits in bioactive drugs.

Approaches to alkylate NH-containing heterocycles have therefore been widely investigated, and the use of methyl iodide [6-8] or dimethyl sulfate [9,10] in the presence of a variety of bases, such as NaH,[11] $NaNH_2$ [12] and NaOH [10] have become classic methods to form *N*-methylated indoles. But most reagents used in these methods are toxic and/or corrosive; hence, their use should be restricted.[13,14] Dimethyl carbonate (DMC) is an attractive alternative. It is a non-toxic green methylating agent, biodegradable, relatively inert and safe to use under ambient conditions.[15-21] DMC synthesis (**Scheme 1**) also employs an eco-friendly oxidative carbonylation of methanol with oxygen.[16]

$$2\,CH_3OH \; + \; CO \; + \; \tfrac{1}{2}O_2 \xrightarrow{\;\textbf{Cu salt}\;} CH_3OCO_2CH_3 \; + \; H_2O$$
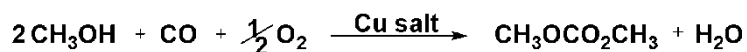
Scheme 1. Formation of dimethyl carbonate (DMC).

N-methylation of indoles,[18,22] imidazoles[22,23] and morpholines[24,25] with DMC are well documented[15] and different nucleophilic amines, such as *N,N*-dimethylpyridin-4-amine (DMAP),[26] *N,N,N',N'*-tetramethylethylenediamine (TMEDA)[27] and 2,4-diaminotoluene have been used as organocatalysts. Phase-transfer catalysts have also been employed.[28]

In 2003, Shieh and co-workers[29] reported on the dualistic nature of 1,4-diazabicyclo[2.2.2]octane (DABCO) as the catalyst for the *N*-methylation of indoles with DMC, proposing a mechanism (**Scheme 2**) that invoked competing alkylation and methoxycarbonylation pathways. Synthetic studies for DMC methylation have shown that DABCO is more effective than most catalysts such as DMAP or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) forming alkylated indole in very high yields.

As **Scheme 2** shows, two key steps and a key cationic carbamate intermediate (**5**) were proposed. In short, the reaction initiates when DMC (**2**) "methoxycarbonylates" DABCO (**3**) to form **5** and CH_3O^- (**4**) as the counter anion. Next, **4** deprotonates indole to form **6** with **5** functioning now as the counter cation. Finally, the nucleophilic attack of **5** by **6** that regenerates the DABCO catalyst (**3**) forms *N*-methylated indole (**7**).
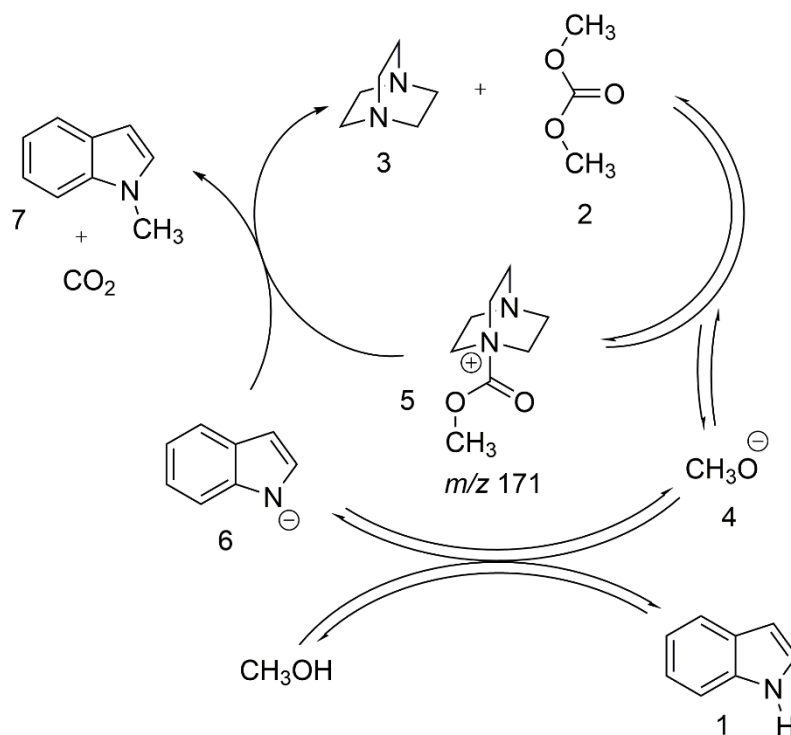
Scheme 2. Mechanism proposed by Shieh[29] for the *N*-methylation of indole with DMC catalysed by DABCO.

We rationalize, however, that depending on the reaction partner, DMC (**2**) could act either as an alkylating or methoxycarbonylating agent, or both (**Scheme 3**). The carbonyl group of DMC is a harder (h) electrophile than its methyl group (s)[30,31]; hence, other mechanisms could operate to give DMC its superior *N*-methylation ability.
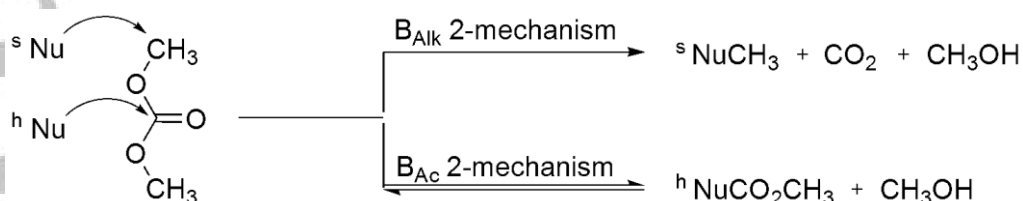
Scheme 3. Expected dual reactivity of DMC as either a soft (s) or harder (h) nucleophile.[8]

Electrospray ionization mass spectrometry (ESI-MS) monitoring[32-35] has been established as powerful tool to study reaction mechanism due to its ability to provide continuous and *in situ* snapshots of the changing composition of ionic species present in reaction solutions. ESI has also been able to transfer, with great gentleness, speed and sensitivity, many ionic reaction intermediates to the gas phase for MS characterization.[36-41] Due to direct and rapid action, ESI has also been efficient in transferring even most short-lived intermediates to the gas phase for MS(/MS) characterization. Many organic reactions or the action of different metal catalysis have been therefore extensively investigated via ESI-MS allowing "ion fishing"[36-41] of multiple intermediates and products.[17,42,43]

Considering the relevance of indole *N*-methylation by DMC, and the need of more evidence to consolidate its divergent mechanisms when either DBU or DABCO are employed, we decided to investigate such reactions via ESI-MS monitoring. Several cationic or anionic intermediates seem to be involved in the actual reaction mechanisms, and neutral but basic species could also be easily protonated, hence ESI(+)MS monitoring looked promising in efficiently intercepting and characterizing the major species involved.

Results and Discussion

ESI(+)-MS monitoring was first conducted up to 8 h with a reaction solution containing indole (**1**, 3.0 mmol), DABCO (**3**, 0.1 equiv.), DMC (**2**, 5.0 mL), and DMF as the solvent (0.5 mL) at 94-95 ºC. Aliquots (0.5 µL) were diluted in acetonitrile with a trace of formic acid, and directly subjected to ESI(+)-MS. Spectra were collected in

different time intervals. **Figure 2** shows three typical ESI(+)-MS for the reaction solution at t_0, 2 h and 7 h. At t_0, ESI(+)-MS was only able to detect protonated molecules of the solvent and the catalyst, that is [DMF + H]$^+$ of m/z 74 and [**3** + H]$^+$ of m/z 113, as well dimers and trimers of solvent and protonated **3** . But fortunately, as **Figures 2b** (2h) and **Figure 2c** (7h) illustrate, after a few hours of reaction, spectra changed dramatically and also continuously allowing the detection of intermediates species that seemed to be key to the reaction mechanism. The major intercepted species were: N-methylated-DABCO (**8**) of m/z 127, **9** of m/z 244, that is [**8** + **1**]$^+$ and **11** of m/z 370, that is [**8** + **8** + **6**]$^+$, in which **6** is deprotonated indole. Other minor and likely less relevant species such as [**8** + **8** + HCO$_2$H]$^+$ of m/z 299, [**8** + **1** + DMF]$^+$ of m/z 317 were also detected. A particularly revealing finding is that **5**, the key intermediate proposed by Shieh (**Scheme 2**), could not be detected at all by ESI(+)-MS, despite the intrinsic cationic nature of this species and hence its expected prompt detection by ESI(+)-MS.
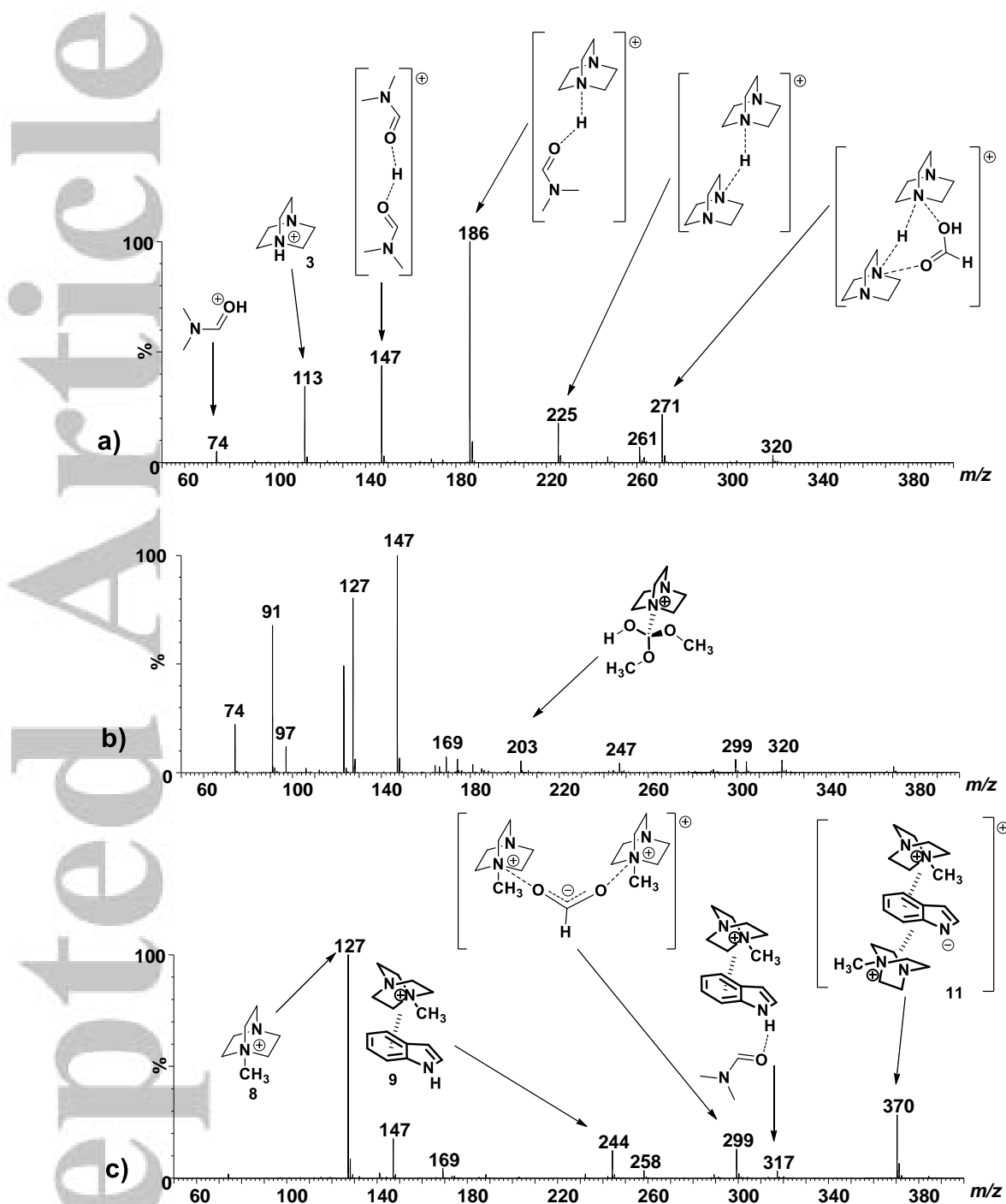
Figure 2. ESI(+)-MS of the reaction solution using DABCO as catalyst at: (**a**) t = 0 h; (**b**) t = 1 h and (**c**) t = 7 h.

To try to characterize the major intercepted ions, collision-induced dissociation (CID) with argon via ESI(+)-MS/MS experiments were conducted (Supporting

Information). Fortunately, the dissociation chemistries observed corroborate the structural assignments of **Figure 2**. The two crucial pieces of information emerging from the ESI(+)-MS monitoring was therefore; first, the failure to detect the Shieh intermediate **5** of *m/z* 171 and, second, the efficient detection of *N*-methylated indole **8** of *m/z* 127, and its association species **9** and **11.** Both **8** and **9** are likely the predominant reaction species directly fished out from the reaction solution.

To rationalize the absence of **5** in the reaction media, and the exclusive and predominant intermediate **8**, theoretical calculations at the B3LYP-D3/6-311+G(d,p) level were performed. The calculations suggest that indeed DMC, when attacked by DABCO at its carbonyl carbon would fail to form **5**, but instead such attack leads favorably to a stable DABCO-DMC zwitterionic adduct (**Figure 3**). Note that this stable adduct was indeed "fished out" by ESI(+)-MS via its protonated form of *m/z* 203 at the early stages of the reaction, notably from 1 h up to 2 h (**Figure 2b**).
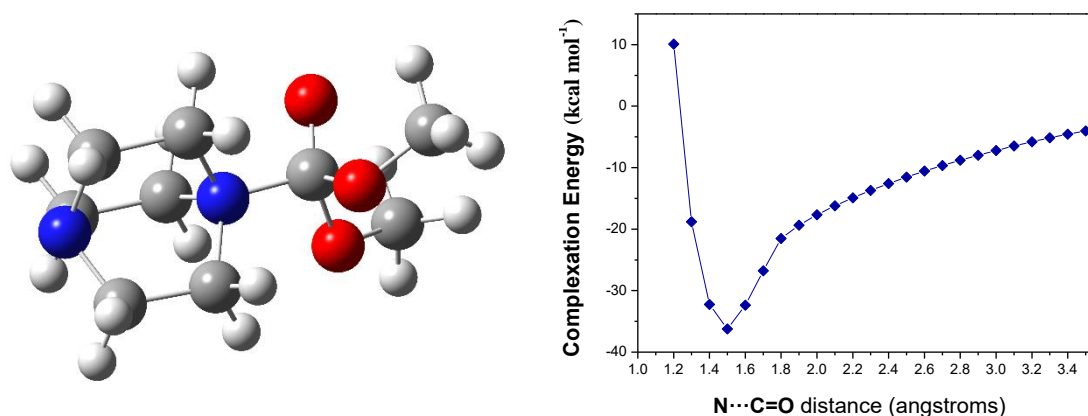

Figure 3. Optimized structure and the potential energy curve (PEC) along the N⋯C=O interaction leading to the stable DABCO.DMC adduct formed by attack of DABCO at the carbonyl carbon of DMC calculated at the B3LYP-D3/6-311+G(d,p) level.

Calculations also predict that if DABCO attacks the methyl carbon of DMC (**Figure 4**), the reaction would proceed to form *N*-methylated DABCO (**8**) via **TS-1** (23.4 kcal mol^{-1}) in a slightly exothermic reaction (*ca.* -2.3 kcal mol^{-1}).
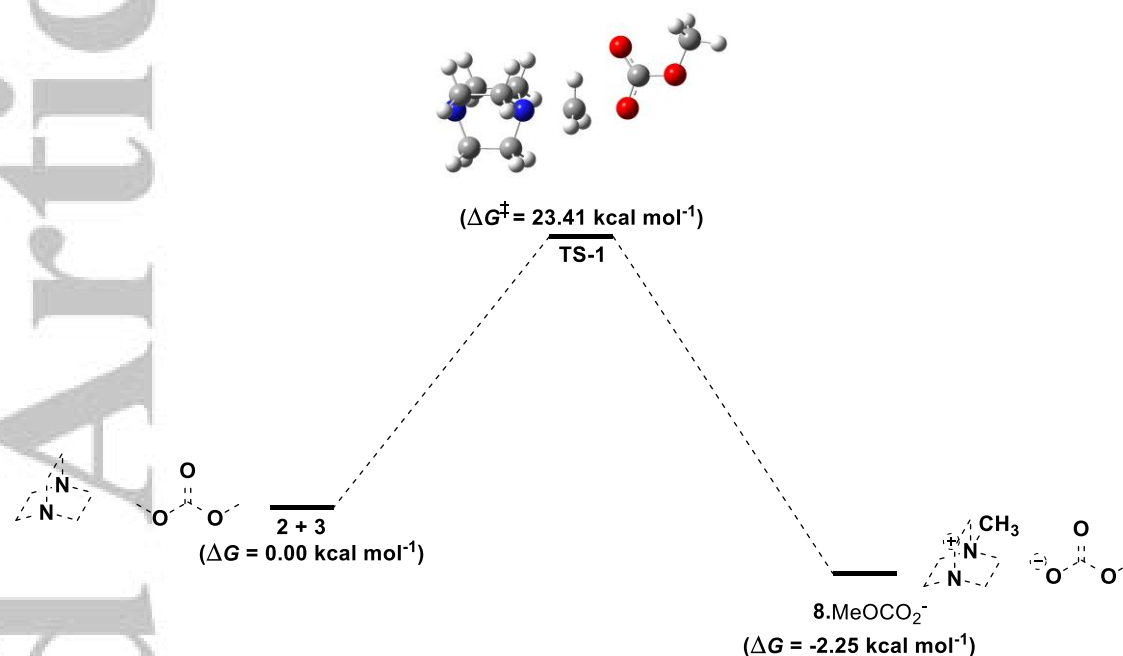
Figure 4. Free-energy diagram for the methylation reaction between DABCO and DMC yielding the cationic *N*-methylated DABCO (**8**) calculated at the B3LYP-D3/6-311+G(d,p) level with implicit DMC solvation.

Based on the combined ESI(+)-MS data and theoretical predictions, we propose a new mechanistic scenario for the *N*-methylation of indole with DMC catalysed by DABCO (**Scheme 4**). Note that all species in our scenario have been corroborated by calculations but more importantly, properly intercepted and characterized by ESI(+)-MS(/MS) monitoring.
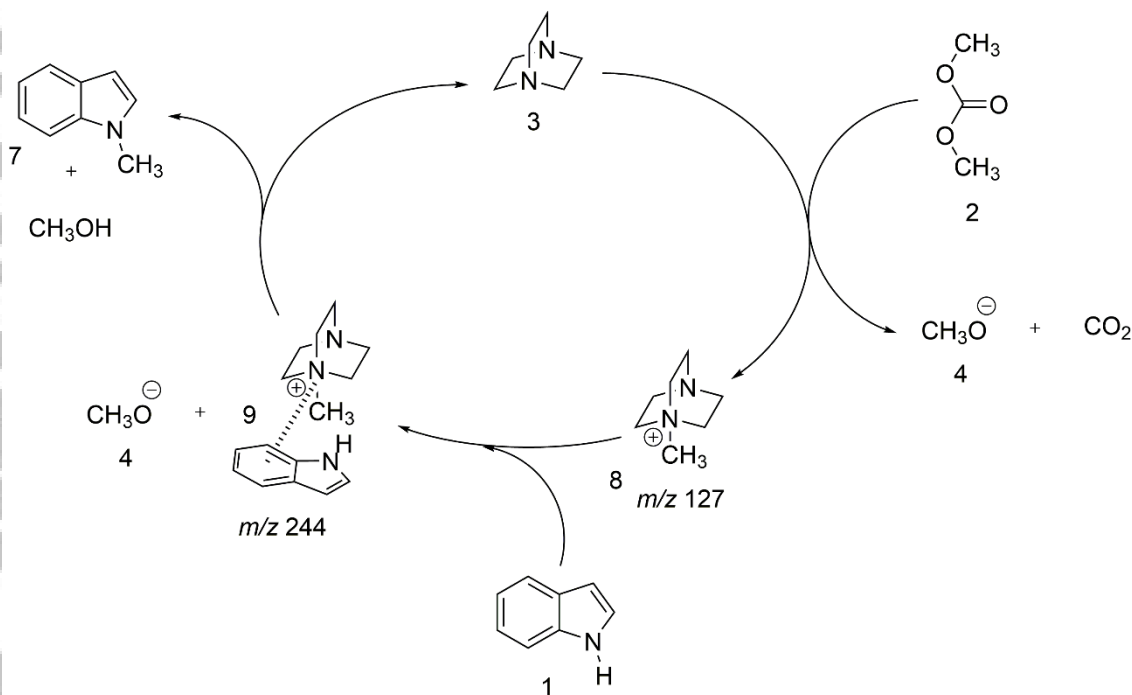
Scheme 4. A new mechanism proposed for the *N*-methylation of indole with DMC catalyzed by DABCO.

The new mechanism of **Scheme 4** starts therefore when the soft nucleophile DABCO (**3**) attacks DMC (**2**) at its methyl group forming *N*-methylated-DABCO (**8**) as the first key cationic intermediate **8** of *m/z* 127. Indole (**1**) coordinates next with **8** to form **9** of *m/z* 244. The methoxy anion (**4**) then attacks **9** abstracting the acidic NH proton from indole to form **10,** as **Scheme 5** rationalizes in more detail. Note that **10** is neutral but fortunately it was detected by ESI(+) in its cationized form **11** of *m/z* 370, that is, as the [**10** + **8**]⁺ adduct. The final product, *N*-methyl indole (**7**) is formed via methyl transfer within the ion-pair **10** returning DABCO (**3**) to the catalytic cycle. Since **11** was also detected, a similar transfer assisted by **8** could also be proposed via **11**.
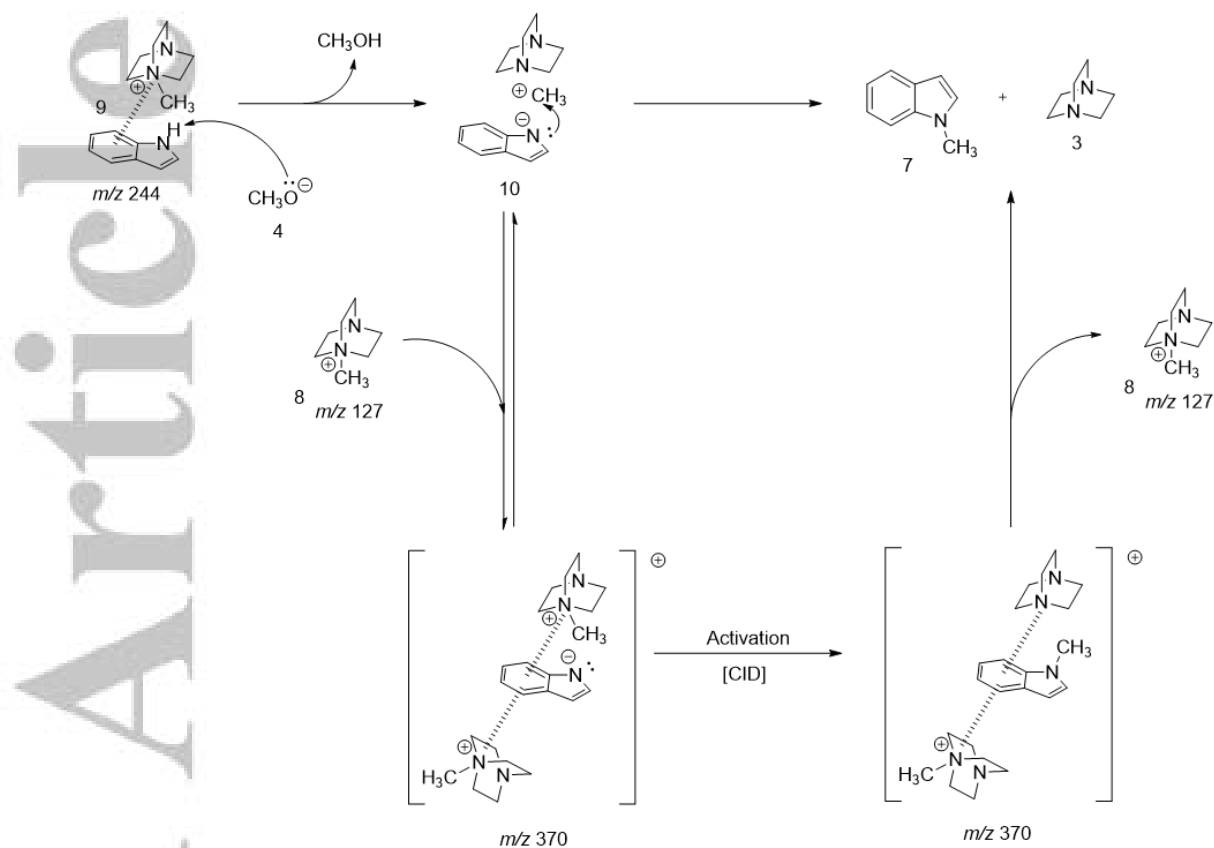
Scheme 5. Detailed mechanistic view for methyl transfer to indole.

The mechanistic proposal of **Scheme 5** has also been further supported by theoretical calculations. As **Figure 5** shows, optimized structures for **9** formed by the association of *N*-methylated DABCO (**8**) and indole (**1**) as well as **11** were found to be quite stable species. The equilibrium geometry for **9** displayed C-H···π distances of *ca.* 2.8 Å and a strong attractive interaction energy of *ca.* -16 kcal mol^{-1} (free energy of formation of **9** from **8** and **1**). An even higher attractive interaction energy was found for **11**, *ca.* -110.5 kcal mol^{-1} (free energy of formation of **11** from **6** and 2 molecules of **8**). This interaction energy is so high because an indole anion (**6**) is sandwiched by two cationic *N*-methylated DABCO moieties (**8**).

Figure 5. Optimized equilibrium geometries of complexes **9** (left) and **11** (right) calculated at the B3LYP-D3/6-311+G(d,p) level. Geometries were calculated with BSSE corrections included and were characterized as true minima with frequency calculations at the same level.

The Gibbs free energy diagram for the reaction of methyl cation transfer occurring within the neutral complex **10** (**Scheme 5**) was also calculated (**Figure 6**). Note that the forward reaction occurs with a relatively low barrier (*ca.* 22.5 kcal mol^{-1}) resulting in a reaction that is exothermic by ΔG = -24.15 kcal mol^{-1}.
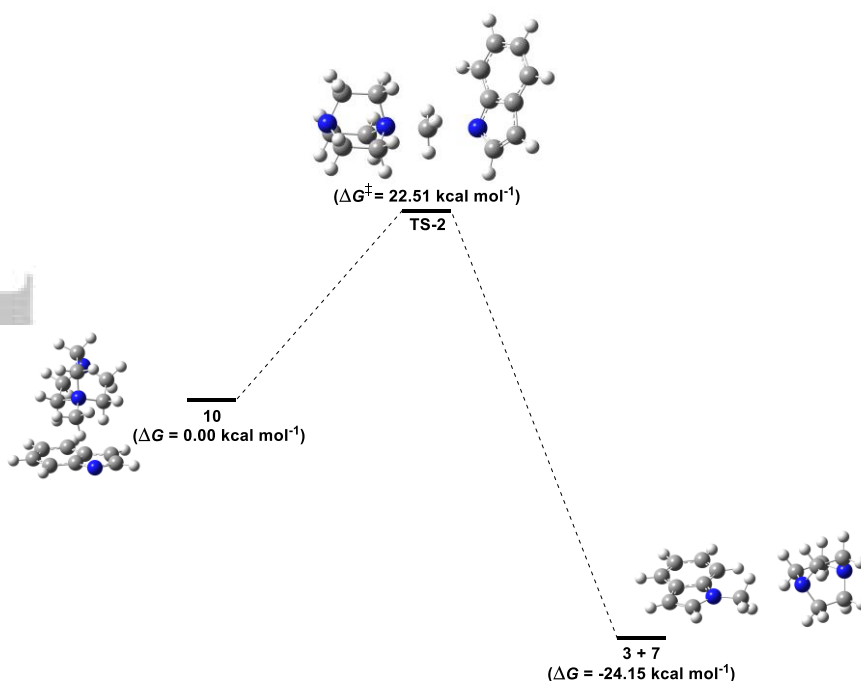

Figure 6. Free-energy diagram for the reaction of *N*-methyl-DABCO (**8**) with deprotonated indole as calculated at the B3LYP-D3/6-311+G(d,p) level with implicit

DMC solvation. It is interesting to note that the minimum found for the starting materials complex was indeed **10**.

For the Shieh mechanism of **Scheme 2**, we also note that the acidity of methanol as measured by its pKa is lower than that of indole, which leads to an unfavorable equilibrium for the deprotonation step (**Scheme 6**).[44] These values are the aqueous acidities, however, and we ran the reaction in DMF. The DMSO pKa's are a much better guide in this instance and they are 29.0 (methanol) and 21.0 (indole), so this would not be a problem in solution.

The formation of **9** (**Scheme 4**) seems therefore crucial to increase the acidity of indole so as to favor NH abstraction by the methoxy anion (**Scheme 5**). This activation was supported by ESI(+)-MS monitoring via the interception and characterization of **11** of m/z 370 (**Figure 2c**), which formally consist of [**10** + **8**].

a) indole
pKa = 17

methanol
pKa = 15.5
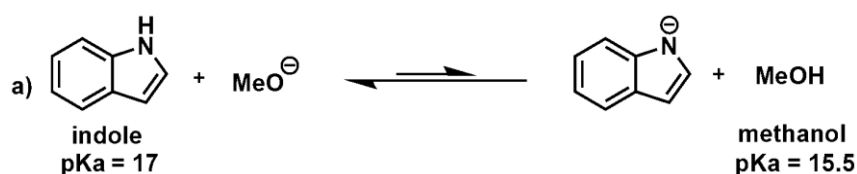
Scheme 6. Unfavorable proton exchange equilibrium between indole and the methoxy anion.

Shieh's[29] also used other bases as catalysts in the *N*-methylation of indole suggesting a common mechanism (regardless of the catalyst) to rationalize also the observation of a second product arising from *N*-methoxycarbonylation. In a second experiment, to investigate therefore whether specific intermediates responsible for the competition between the *N*-methylation and *N*-methoxycarbonylation routes could be intercepted, we employed DBU as the catalyst.[22] Note that Shieh's observations

suggest that *N*-methoxycarbonylation is kinetically favored but ultimately irreversible *N*-methylation drives product formation.[45]

For DBU, we used the same experimental conditions as for the reaction with DABCO. **Figure 7** shows three typical ESI(+)-MS spectra for the DBU-catalysed reaction.
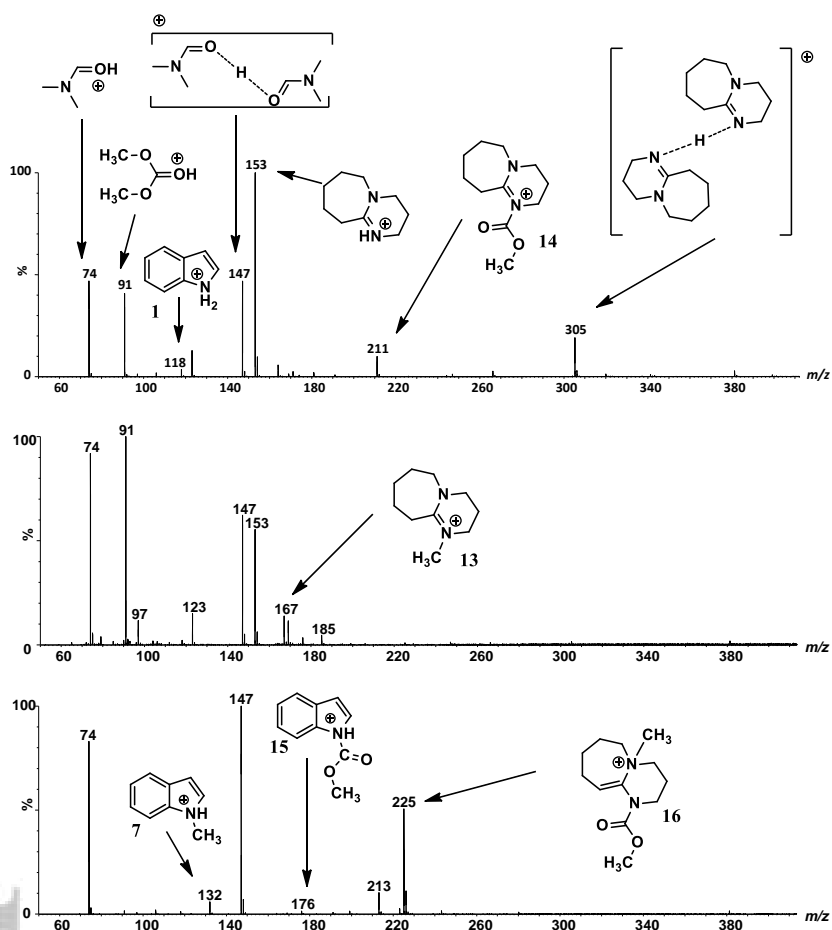
**Figure 7.** ESI(+)-MS of the reaction solution using DBU as the catalyst at: (**a**) *t* = 0 h; (**b**) *t* = 1 h and (**c**) *t* = 7 h.

Note that indeed key species seem to have been intercepted; mainly **13** of *m/z* 167, **14** of *m/z* 211 and **16** of *m/z* 225, as well as the both the two final products **7** of *m/z* 132 and **15** of *m/z* 176. We further characterized these intermediates and products

via ESI-MS/MS (**Figures S38** and **S39**). In 2011, Quaranta *et al.*[46] studied the reaction between dimethyl carbonate and DBU, directly addressing the relevance and behavior of **14**. Additionally, they suggested an approach to synthesize proposed intermediate **16**, since they synthesize the *N*-alkoxy-carbonyl ketene aminal.

Based on these intercepted ESI(+)-MS and MS/MS characterized intermediates and products, we propose in **Scheme 7** a rationale for the reaction mechanism leading to both *N*-methylation and *N*-methoxycarbonylation of indole with DMC catalyzed by DBU. Note that we suggest that *N*- methoxycarbonylation is promoted by **14** and **16** whereas **13** and **16** promotes *N*-methylation. Intermediate **16** of *m/z* 225 accumulates from **14** of *m/z* 211 (compare **Figures S29** and **S30**). Quaranta *et al.* [46] also observed formation of **13** and **16** by mass spectrometry via the reaction of pyrrole with dimethyl carbonate under phosphazene catalysis, but they failed to fully rationalize the importance of thse findings.
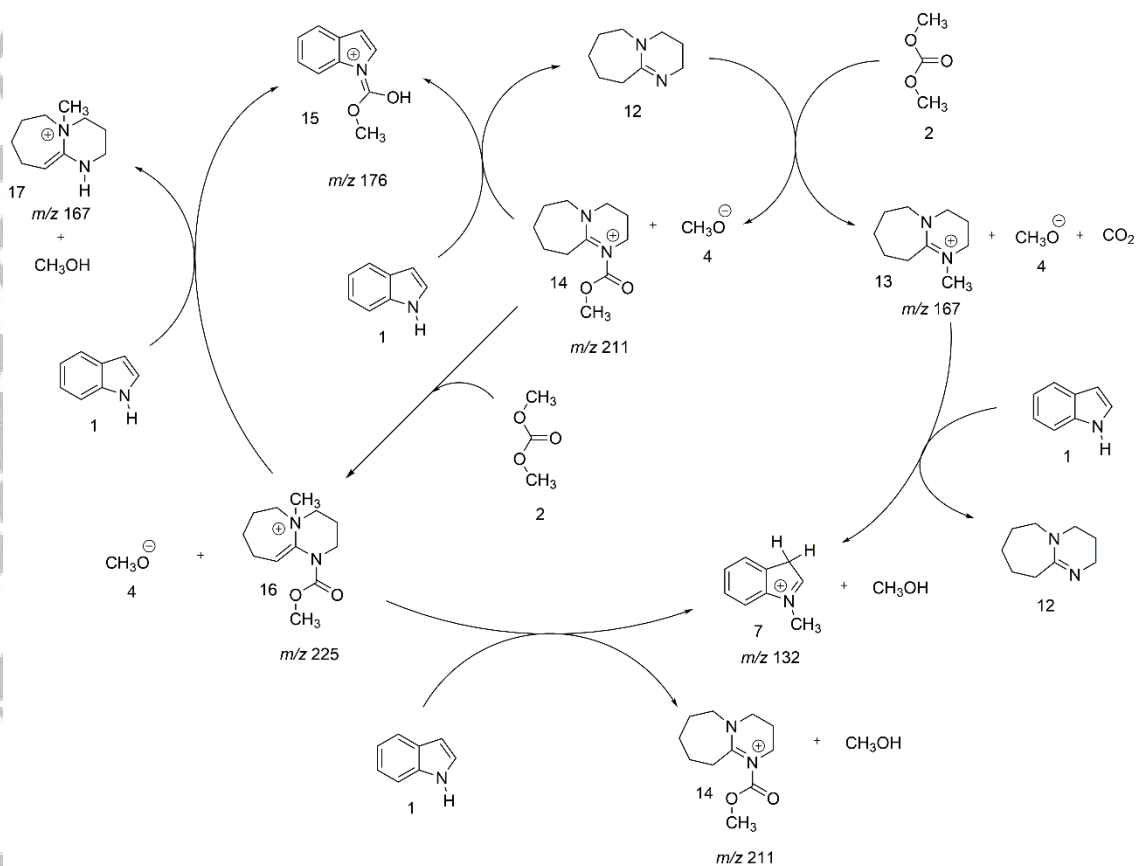
Scheme 7. New mechanistic proposal for the competition between *N*-methylation and *N*-methoxycarbonylation of indole with DMC when DBU is used as the catalyst.

Conclusions

By combining data from ESI(+)-MS(/MS) monitoring and theoretical calculations, we have unveiled the mechanisms operating when indole is methylated by DMC in the presence of either DABCO or DBU as the catalyst. When DABCO is used, the reaction forms exclusively *N*-methylated indole and we propose that the methyl transfer occurs via a complex formed between *N*-methylated DABCO and indole. But with DBU, two competitive mechanisms operate and indole undergoes both *N*-methylation as well as *N*-methoxycarbonylation. Accounting for this competition, we

intercepted and characterized three key intermediates, and have herein proposed a detailed and unified mechanistic view.

Experimental

General remarks

All reagents were used without purification. Mass spectrometry data: ESI mass and tandem mass spectra in the positive ion mode using a mass spectrometer Micromass (Manchester, UK) QTof instrument of ESI-QTof configuration with 5000 mass resolution and 50 ppm mass accuracy in the TOF mass analyzer.[47] The following typical operating conditions were used: 3 kV capillary voltage, 8 V cone voltage and desolvation gas temperature of 100 ℃. Tandem ESI-MS/MS were collected after 4-32 kV collision-induced dissociation (CID) of mass-selected ions with argon. Mass-selection was performed by Q1 using a unitary *m/z* window and collisions were performed in the rf-only hexapole collision cell, followed by mass analysis of product ions by the high-resolution orthogonal reflectron TOF analyser. ESI(+)-MS/MS data were processed via the MassLynx software v4.1.

General procedure for the *N*-methylation of indole with dimethylcarbonate catalysed by DABCO or DBU (reaction monitoring)

A reaction flask was charged with an indole (500 mg), DABCO or DBU (0.1 eq.), DMF (0.5 mL) and dimethylcarbonate (5.0 mL). The mixture, in inert atmosphere, was heated to 95 ℃ and the reaction was monitored by ESI-(+)-MS during 8 h. Aliquots from reactions medium (1 µL) were continuously taken and diluted in 1 mL of

acetonitrile (ACN). The sample solutions were prepared in polypropylene microtubes (Eppendorf®) and directly injected into the ESI(+)-QTOF.

Theoretical Calculations

All calculations were carried out using the Gaussian 16 program, Revision C.01.[44] All DFT calculations were run at the B3LYP/6-311+G(d,p) level of theory employing Grimme's DFT-D3 dispersion corrections.[48] For complexes **9** and **11**, BSSE corrections were included using the counterpoise method.[49,50] All minima were characterized as true minima by frequency calculations at the same level of theory having no negative harmonic vibrational frequencies. The transition state (TS) geometries were characterized by the observation of a single negative harmonic vibrational frequency for each TS. The harmonic frequencies were also used to obtain thermodynamic corrections to Gibbs free energies at 298.15 K and 1 atm. Even though the reactions were run at a higher temperature, the calculations were done at standard temperature due to the small impact the temperature had on the activation energy of the reactions. All transition states were submitted to intrinsic reaction coordinates (IRC) calculations at the same level of theory. Solvent effects were taken into account by running single point calculations on the gas phase optimized structures using the integral equation formalism variant of the Polarizable Continuum Model (IEFPCM)[51] using DMC as the solvent ($\varepsilon = 3.108$).[52] DMC was chosen as model solvent because it is the main component of the reaction mixture. Results with the parameters for DMF are deposited in the ESI. Final free energies were obtained by adding the thermodynamic corrections evaluated in the gas phase to these single point energies in the continua. The Cartesian coordinates, energies, first harmonic vibrational frequency, and IRC plots are available in Supporting Information.

Funding

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Graphical Abstract
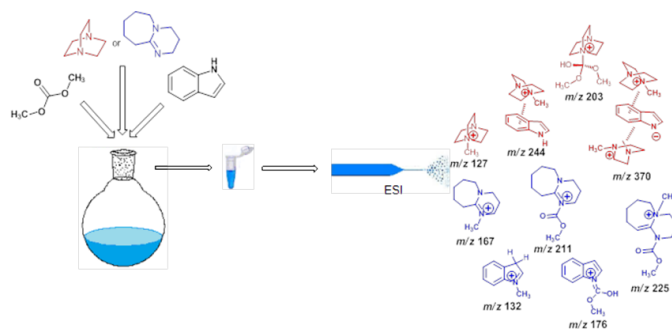
Using direct ESI(+)-MS monitoring to collect actual snapshots of the changing ionic composition of the reaction solution, we report on the interception and characterization of key intermediates for such reactions. Although a mechanism has been proposed with the key intermediate being the same methoxycarbonylated base for both DBU and DABCO, the ESI(+)-MS data as well as B3LYP-D3/6-311+G** calculations suggest that the reaction of DMC with indole follow contrasting mechanisms under either DABCO or DBU catalysis.