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Charge-transfer complexation of TCNE with azithromycin, the antibiotic used worldwide to treat the coronavirus disease (COVID-19). Part IV: A comparison between solid and liquid interactions

Abdel Majid A. Adam a,⇑, Moamen S. Refat a, Tariq A. Altalhi a, Khaled Saleh Alsuhaibani b

a Department of Chemistry, College of Science, Taif University, P.O. Box 11099, Taif 21944, Saudi Arabia
b College of Pharmacy, King Saud University, Riyadh, Saudi Arabia

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A B S T R A C T
Finding a cure or vaccine for the coronavirus disease (COVID-19) is the most pressing issue facing the world in 2020 and 2021. One of the more promising current treatment protocols is based on the antibiotic azithromycin (AZM) alone or in combination with other drugs (e.g., chloroquine, hydroxychloroquine). We believe gaining new insight into the charge-transfer (CT) chemistry of this antibiotic will help researchers and physicians alike to improve these treatment protocols. Therefore, in this work, we examine the CT interaction between AZM (donor) and tetracyanoethylene (TCNE, acceptor) in either solid or liquid forms. We found that, for both phases of starting materials, AZM reacted strongly with TCNE to produce a colored, stable complex with 1:2 AZM to TCNE stoichiometry via a n → π* transition (AZM → TCNE). Even though both methodologies yielded the same product, we recommend the solid–solid interaction since it is more straightforward, environmentally friendly, and cost- and time-effective.

1. Introduction

A charge transfer (CT) interaction, commonly referred to as a CT reaction or CT complexation, involves one molecule donating electrons to another molecule [1–8]. The former donor (D) molecule is electron-rich while the latter acceptor (A) molecule is electron-deficient. The chemistry of CT interactions has received considerable interest from researchers year after year because it yields new complexes with unique chemical and physical properties that render them beneficial to pharmacology, medicine, industry, and academia (biology, physics, biochemistry, and chemistry). Many synthesized CT complexes have high electrical conductivity/super conductivity and strong magnetism, and, therefore, contribute to many important electrical conductor, superconductor, optoelectronic, light-emitting, and solar energy storage devices [9–23]. Moreover, countless synthesized CT complexes exhibit promising antitumor, anti-inflammatory, and antimicrobial properties. CT interactions are used to study and understand biological processes in the human body (e.g., DNA binding, enzymatic reactions) and the thermodynamics and pharmacodynamics of therapeutic compounds (e.g., mechanism of action, drug delivery) [24–32]. Every year, considerable research efforts are dedicated to producing new CT complexes, investigating their properties (e.g., photophysical, thermodynamic, crystallographic, spectral, kinetic), and determining which factors affect the CT interactions (e.g., type of solvent, time, concentration, temperature) [18,33–53].

Azithromycin (AZM; C38H72N2O12, 748.98 g/mol; Fig. 1) is an orally bioactive, highly effective, well-tolerated, broad-spectrum antibiotic used to treat infectious diseases caused by both Gram-positive and Gram-negative bacteria. In addition to its antibacterial properties, AZM also has antimalarial, anti-inflammatory, immunomodulatory, and antiviral effects [54–57]. AZM caught the world’s attention in 2020 because it showed promising results in the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) disease, commonly known as COVID-19. This syndrome was first identified in Wuhan, China on December 9, 2019, and spread swiftly throughout China and around the globe [58]. By early March 2020, the World Health Organization (WHO) declared the COVID-19 outbreak a pandemic [59]. At that point, the global rush began to find means to conquer this pandemic and stop its psychological, medical, and economic burdens [60]. AZM has been incorporated into the treatment protocols for COVID-19 alone and in conjugation with other drugs (e.g., chloroquine, hydroxychloroquine). This protocol is clinically effective and now widely used around the world as a short-term course [61–66].

We believe providing new insight into the CT chemistry of AZM will help researchers and physicians alike to improve the treat-
ment protocols for COVID-19. As a continuation of our previous works [67–69] that aim to furnish a big-picture perspective on the CT chemistry of azithromycin by examining its complexation with several acceptors (σ- and π-) and the resultant CTCs, in this work, we examine the CT interaction between AZM (donor) and tetracyanoethylene (TCNE; acceptor) in both the solid–solid and liquid–liquid states. The solid–solid interaction generated a solid CT complex by grinding solid AZM and TCNE powders together without adding any solvents, while the liquid–liquid interaction also resulted in a solid CT complex but by mixing acetonitrile solutions of AZM and TCNE and filtering off the formed precipitate.

2. Materials and methods

2.1. Materials

The AZM powder (C_{24}H_{72}N_{6}O_{12}; 748.98 g/mol; purity ≥ 98%), tetracyanoethylene (TCNE) (C_{6}N_{4}; 128.1 g/mol; purity 96%), and acetonitrile (CH_{3}CN; 41.05 g/mol; purity 99.8%) were all analytical grade, procured from the Sigma-Aldrich Chemical Company (USA) at the highest purity available, and used as received. AZM and TCNE were completely dissolved in CH_{3}CN solvent.

2.2. Characterization methods

The UV–visible absorption spectra and the FT-IR spectra were measured using a DR6000 Benchtop HACH Lange UV/VIS Spectrophotometer (200–800 nm) and IR Tracer-100 Shimadzu Fourier-Transform Infrared Spectrophotometer, respectively. The nitrogen, hydrogen, and carbon composition (in percentages) were determined using a PE 2400 Series II Perkin-Elmer CHN Microanalyzer.

2.3. Synthetic methods

2.3.1. Product 1

Product 1 was generated by grinding solid AZM and TCNE powders together without adding any solvent [35,70–72]. Specifically, 0.749 g of AZM (1 mmol) and 0.256 g of TCNE (2 mmol) were put in a dry, clean porcelain mortar. Then, the two components were ground together thoroughly using a pestle for 5 min until a uniform, solid powder was generated. Finally, the obtained yellow homogenate, termed Product 1, was collected and stored in a vacuum desiccator with CaCl_{2} (anhydrous) at room temperature to protect it from humidity. FT-IR and elemental analyses were used to characterize the product. IR data: 3485 and 3251 ν(O–H), 2974 ν_{asym}(CH_{3}), 2938 ν_{asym}(CH_{2}), 2890 ν_{sym}(CH_{2}), 2830  ν_{sym}(CH_{2}), 2200 and 2262 ν(C≡N) 1718 ν_{asym}(C≡O), 1595 ν_{sym}(C≡O), 1500 ν (C=C), 1461 δ_{rock}(CH_{3}), 1374 δ_{sciss}(CH_{3}), 1276 δ_{rock}(CH_{2}), 1165 ν_{asym}(C=N), 1080 ν_{sym}(C=N), 1041 ν(C=O), 995 ν(C≡C), 900 δ (O–H) in-plane bending, 800 δ_{wag}(CH_{2}), 731 ν(O–H) out-of-plane bending, and 558 δ_{sciss}(CH_{2}). Elemental data (%): yellow powder; C_{24}H_{72}N_{6}O_{12} (877.1 g mol⁻¹); observed (calculated) for N, 9.35 (9.58); H, 8.42 (8.21); C, 59.92 (60.20).

2.3.2. Product 2

Product 2 was generated by mixing acetonitrile solutions of AZM and TCNE and filtering off the formed precipitate [73–76]. Specifically, solutions of AZM (1 mmol in 20 mL CH_{3}CN) and TCNE (2 mmol in 20 mL CH_{3}CN) were mixed thoroughly using a magnetic stirrer for 15 min at room temperature. The volume of the mixture was reduced by half using a water bath, then left for 24 h at room temperature to ensure complete precipitation. The resultant yellow precipitate was filtered through Whatman 42 grade filter paper, washed thoroughly using CH_{3}CN solvent, and then dried in a vacuum desiccator with CaCl_{2} (anhydrous) at room temperature for 48 h. The resultant product was termed Product 2 and characterized using FT-IR and elemental analyses. IR data: 3442 and 3227 ν(O–H), 2973 ν_{asym}(CH_{3}), 2933 ν_{asym}(CH_{2}), 2885 ν_{sym}(CH_{3}), 2830 ν_{sym}(CH_{2}), 2198 and 2163 ν(C≡N) 1721 ν_{asym}(C≡O), 1594 ν_{sym}(C≡O), 1500 ν(C≡C), 1462 δ_{rock}(CH_{2}), 1380 δ_{sciss}(CH_{2}), 1263 δ_{rock}(CH_{3}), 1165 ν_{asym}(C≡N), 1092 ν_{sym}(C≡N), 1000 ν(C≡O), 950 ν(C≡C), 890 δ(O–H) in-plane bending, 803 δ_{wag}(CH_{2}), 720 ν(O–H) out-of-plane bending, and 620 δ_{sciss}(CH_{2}). Elemental data (%): yellow powder; C_{24}H_{72}N_{6}O_{12} (877.1 g mol⁻¹); observed (calculated) for N, 9.77 (9.58); H, 8.50 (8.21); C, 59.98 (60.20).

3. Results and discussion

3.1. CT absorption

The generation of a CT complex is typically associated with a strong color change upon combining the donor and acceptor. Therefore, UV–visible spectroscopy is the conventional technique used to detect such changes and to determine whether a CT interaction occurred and to characterize this interaction. The CT interaction alters the electronic absorption spectrum of the donor, acceptor, or both and this is reflected by the change in color. These spectral changes fall into two categories:

(i) Hypsochromic shifts: the appearance of a new absorption band in the UV–visible spectrum of the resultant CT complex where neither the free donor nor acceptor have any measurable absorption.

(ii) Bathochromic shifts: increases in intensity and/or size of the absorption band that characterized the donor, acceptor, or both.

In this work, upon mixing the solutions of AZM (10 × 10⁻³ M; colorless in CH_{3}CN solvent) and TCNE (10 × 10⁻³ M; pale brown in CH_{3}CN solvent), a strong color change was observed from pale brown to intense yellow color in the resultant CT complex, as pictured in Fig. 2. This type of color change is suggestive of a strong CT interaction between AZM and TCNE. Fig. 3 contains the UV–visible absorption of the AZM (5.0 × 10⁻⁴ M), TCNE (5.0 × 10⁻⁴ M), and the CT complex derived by mixing the two solutions (1:1). The solution of free AZM is CH_{3}CN solvent, which is colorless, with no measurable absorption bands in the UV–visible region. The solution of free TCNE in CH_{3}CN solvent was pale brown, with a broad absorption band ranging from 354 to 440 nm with a long tail ranging from 440 to 800 gradually decreasing in intensity. The broad band had two maximum heads at 395 and 414 nm. After TCNE complexed with AZM, the intensity of the broad band that characterized free...
TCNE increased greatly and became a little much broader. These two heads were still present at the same positions but became clearer and sharper. The long tail was absent and, instead, a small weak band appeared at 463 nm. These spectral changes indicated bathochromic shifts occurred when AZM formed a CT complex with TCNE.

3.2. Product 1

Product 1 was generated through a solvent-free solid–solid interaction using a simple one-step method. Solid AZM (1 mmol) and TCNE (2 mmol) were ground together thoroughly in a porcelain mortar. AZM reacted with TCNE without any solvent to form a yellow-colored solid homogenate (Product 1), as pictured in Fig. 4. As shown in Fig. 4, solid AZM alone is white, solid TCNE alone is black, and grinding them together produced a yellow-colored product. This strong color change indicates that a CT complexation reaction occurred between the AZM and TCNE molecules through a solvent-free, solid–solid interaction. Fig. 5 shows the color of Product 1 (yellow) and Product 2 (yellow–brown). A sample of Product 1 was elementally characterized. The obtained values for the N%, H%, and C% were 9.35%, 8.42%, and 59.92%, respectively. These data agree with the values calculated theoretically from the molecular formula of Product 1 (C44H72N6O12; 877.1 g mol⁻¹), (calculated values 9.58%, 8.21%, and 60.20%, respectively). The elemental composition of Product 1 confirmed that the solid–solid interaction between AZM and TCNE proceeded at a molar ratio of 1:2 (AZM to TCNE). A solution of Product 1 was prepared in CH₃CN solvent at a concentration of 5.0 × 10⁻⁴ M and scanned by UV–visible spectroscopy; the resulting electronic absorption spectrum is presented in Fig. 6. The UV–visible absorption spectrum of Product 1 was characterized by a very strong, broad band ranging from 345 to 480 nm with two maximum heads at 395 and 414 nm. A shoulder band was also detected at 463 nm. The shape of the UV–visible absorption spectrum of Product 1 was similar to that of the CT complex produced by mixing solutions of AZM (5.0 × 10⁻⁴ M) and TCNE (5.0 × 10⁻⁴ M) (Fig. 3), confirming that the solvent-free, solid–solid approach produced a solid AZM-TCNE CT complex.

3.3. Product 2

Product 2 was generated from liquid-phase starting materials using a multi-step process involving a brief reaction period (~3 min), precipitate formation (~24 h), and product filtration and purification. As pictured in Fig. 5, this methodology resulted in a yellow–brown product. The elemental composition of Product

Fig. 2. Strong color change upon mixing TCNE (far left; pale brown) with AZM (middle; colorless) to produce the CT complex (far right; intense yellow) in the CH₃CN solvent.

Fig. 4. Photograph of (A) AZM (up, white) and TCNE (down, black); (B) the resultant Product 1 after grinding the two components for 5 min.
was N 9.77%, H 8.50%, and C 59.98%, which aligned with the theoretical values (N 9.58%, H 8.21%, C 60.20%) calculated from its molecular formula (C₄₄H₇₂N₆O₁₂; 877.1 g mol⁻¹). These results confirmed that the liquid–liquid interaction of AZM and TCNE proceeded via a 1:2 AZM to TCNE molar ratio, as did the solid–solid interaction. A solution of Product 2 was prepared in CH₃CN solvent at 5.0 × 10⁻⁴ M to determine its electronic absorption spectrum. As shown in Fig. 6, the shape of the UV–visible absorption spectrum of Product 2 is similar to that of the CT complex generated by mixing solutions of AZM (5.0 × 10⁻⁴ M) and TCNE (5.0 × 10⁻⁴ M) (Fig. 3). Both spectra contained a very strong, broad band ranging from 345 to 440 nm, with two maximum heads at 395 and 414 nm. A weak shoulder band was also detected at 463 nm. This confirmed that the liquid–liquid methodology produced a solid CT complex of AZM and TCNE. There were two differences in the UV–visible absorption spectra of the two products: i) in Product 2, the width of the band was less than that of Product 1 by 40 nm; and ii) in Product 2, the intensity of the shoulder band at 463 nm was weaker than that of Product 1. These two differences in the electronic absorption spectra are reflected in the product’s color (yellow Product 1, yellow–brown Product 2).

3.4. IR measurements

Fig. 7 contains the FT-IR spectra of the free reactants (AZM and TCNE) and the FT-IR spectra of Product 1 and Product 2 are given in Fig. 8. The IR spectral data (in cm⁻¹) collected for the free AZM molecule were: 3490 and 3245 ν(O–H), 2971 νsym(CH₃), 2932 νasym(CH₂), 2883 νsym(CH₃), 1719 νasym(C=O), 1660 νsym(C=O), 1465 δrock(CH₃), 1377 δsciss(CH₂), 1269 δrock(-CH₂), 1181 νasym(C=O), 1083 νsym(C=O), 1040 ν(C=O), 992 ν(C=C), 836 δ(0–H) in-plane bending, 786 δwag(CH₃), 797 δwag(CH₂), 737 ν(O–H) out-of-plane bending, and 570 δtwist(CH₂) (Fig. 7a). The AZM molecule contains five hydroxyl groups that produced three characteristic bands at 895, 737, and 3490–3245 cm⁻¹ due to their in-plane bending, out-of-plane bending, and stretching vibrational modes. The AZM molecule contains 14 methyl groups (CH₃) that produced four characteristic bands at 2883, 2971, 1465, and 836 cm⁻¹ due to the νsym(CH₃), νasym(CH₃), δrock(CH₃), and δwag(CH₂) modes, respectively. Also, the AZM molecule contains five methylene groups (CH₂). Their asymmetric and symmetric stretching vibrations gave bands at 2932 and 2834 cm⁻¹.
shifted to a lower frequency (2200 cm\(^{-1}\) in Product 1, 2198 cm\(^{-1}\) in Product 2). The absorption band observed at 1181 cm\(^{-1}\) from the \(\nu_{asym}(C\equiv N)\) vibration of free AZM shifted to 1165 cm\(^{-1}\) in both products after complexation with TCNE. This shift implicates nitrogen atoms in the CT bonding between AZM and TCNE. The changes to the \(\nu(C\equiv C)\) bands of free TCNE and \(\nu_{asym}(C\equiv N)\) bands of free AZM observed in their products (Product 1 and Product 2) suggested that the charge transferred from the N-atoms in the AZM molecule to the C≡C moiety of the TCNE molecule, which represents a direct \(n \rightarrow \pi^*\) transition, as proposed in Fig. 9 [35,51,78–80].

3.5. Comparison between the methodologies

A colored, solid CT complex between the AZM and TCNE molecules was synthesized using two methodologies that differed by the phase of the starting materials (solid–solid vs liquid–liquid). The data collected in this study support that both methodologies successfully produced the intended AZM-TCNE CT complex through a direct \(n \rightarrow \pi^*\) transition (AZM → TCNE). Generating this complex using the solid–solid approach is simpler and faster because it is a one-step process that, unlike the liquid–liquid approach, does not require solvents or a purification process. As such, the liquid–liquid methodology is more complex, costly, and time-consuming than its solid–solid counterpart. Table 1 contains a comparison of the two methodologies.

4. Conclusions

After the WHO declared the COVID-19 outbreak a pandemic, a global race began to stop its spread and the associated psychological, medical, and economic burden by finding a cure or vaccine for this disease. Several antibiotics have been tested, current treatment protocols for COVID-19 involve the antibiotic azithromycin (AZM) alone or in combination with other compounds. Giving a vision to the charge-transfer (CT) chemistry of AZM may help clinicians and researchers to improve the treatment protocols for COVID-19. Comparing the CT interactions between AZM donor and TCNE acceptor molecules achieved using two approaches (solid–solid and liquid–liquid) revealed that the former reacts strongly with the latter to produce a colored, stable complex regardless of whether the phase of the starting materials is solid or liquid. Under both conditions, the interaction between AZM and TCNE is a \(n \rightarrow \pi^*\) transition (AZM → TCNE) that proceeds with 1:2 AZM to TCNE stoichiometry. The solid–solid approach is preferable over the liquid–liquid one because it is a simpler, faster means respectively. Their bending vibrations, twisting, wagging, rocking, and scissoring, produced bands at 570, 797, 1269, and 1377 cm\(^{-1}\), respectively. The very strong band resonating at 1040 cm\(^{-1}\) resulted from the \(\nu(C\equiv O)\) vibration. The sharp, medium-strong band at 1719 cm\(^{-1}\) was assigned to the \(\nu_{asym}(C\equiv O)\) vibrational mode, while the broad, weak band located at 1660 cm\(^{-1}\) was attributed to the \(\nu_{sym}(C\equiv O)\) mode. The IR spectrum of the free TCNE molecule (Fig. 7b) had absorption bands with wavenumbers 563, 684, 800, 952, 1152, 1575, (2219 and 2256), and 3217 cm\(^{-1}\) attributed to the vibrational motions of \(\delta_{asym}(C\equiv C)\), \(\delta_{asym}(C\equiv C)\), \(\delta_{sym}(C\equiv C)\), \(\nu_{asym}(C\equiv C)\), \(\nu_{sym}(C\equiv C)\), \(\nu_{asym}(C\equiv C)\), \(\nu_{sym}(C\equiv C)\), \(\nu_{asym}(C\equiv C)\), \(\nu_{sym}(C\equiv C)\), and \(\nu_{asym}(O\equiv H)\), \(\nu_{sym}(O\equiv H)\), \(\nu_{asym}(O\equiv H)\), respectively [77]. The IR spectra of Product 1 and Product 2 (Fig. 8) contained all of the principal bands of the AZM and TCNE molecules, and, in general, the two products exhibited similar IR spectra. The \(\nu(C\equiv C)\) vibration of free TCNE resonated as a very strong band at 1575 cm\(^{-1}\). After complexation with AZM, the intensity of this band decreased and shifted to a lower frequency (1500 cm\(^{-1}\) in both Product 1 and Product 2). The displacement of the \(\nu(C\equiv C)\) vibration by about ~75 cm\(^{-1}\) suggests that the C≡C moiety of the TCNE molecule participated in the CT bonding with AZM. The \(\nu(C\equiv N)\) vibration of free TCNE conferred a medium-strong band at 2219 cm\(^{-1}\) with a shoulder band at 2256 cm\(^{-1}\). After TCNE interacted with AZM, this band

![Fig. 7 (continued)](image)

![Fig. 8. FT-IR spectra of Product 1 and Product 2.](image)

![Fig. 9. Proposed chemical structure of Product 1 and Product 2.](image)
of yielding the same product and, therefore, more time-efficient, cost-effective, and eco-friendly. Complexation between AZM and acceptor molecules can be achieved easily through solid–solid interaction and may improve the efficacy of this antibiotic against specific infections, such as that causing the COVID-19 pandemic.

CRediT authorship contribution statement
Abdel Majid A. Adam: Data curation, Funding acquisition, Investigation, Project administration, Supervision, Writing – original draft, Writing – review & editing. Moamen S. Refat: Data curation, Funding acquisition, Investigation, Project administration, Supervision, Writing – original draft, Writing – review & editing. Tarqi A. Altalhi: Conceptualization, Formal analysis, Methodology, Resources, Software, Validation, Visualization. Khhaled Saleh Alsuhaimani: Conceptualization, Formal analysis, Methodology, Resources, Software, Validation, Visualization.

Declaration of Competing Interest
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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