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Spectroscopic investigations of the charge-transfer interaction between the drug reserpine and different acceptors: Towards understanding of drug–receptor mechanism

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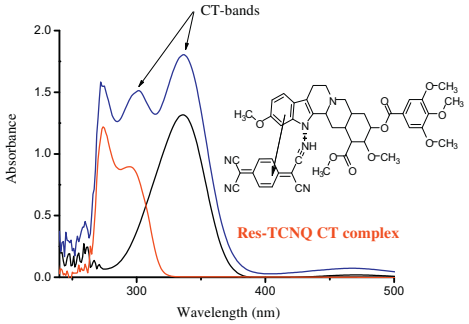
HIGHLIGHTS

- Reserpine (Res) is a biologically active naturally occurring drug.
- Four new charge-transfer complexes of Res were reported for the first time.
- Bonding modes were ascertained from various spectral techniques.
- The obtained complexes are nanoscale and thermally stable.

GRAPHICAL ABSTRACT



Electronic absorption spectrum of Res-TCNQ CT complex

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ABSTRACT

The study of the charge-transfer interaction of the drugs may be useful in understanding the drug–receptor interactions and the mechanism of drug action. Structural and thermal stability of charge-transfer (CT) complexes formed between the drug reserpine (Res) as a donor and quinol (QL), picric acid (PA), tetracyanoquinodimethane (TCNQ) or dichlorodicyanobenzoquinone (DDQ) as acceptors were reported. Elemental analysis, electronic absorption, spectrophotometric titration, IR, Raman, ^{1}H NMR and X-ray powder diffraction (XRD) were used to characterize the new products. The thermal stability of the synthesized CT complexes was investigated using thermogravimetric (TG) analyses, and the morphology and particle size of these complexes were obtained from scanning electron microscopy (SEM). The stoichiometry of the complexes (donor:acceptor molar ratio) was determined to be 1:1 for all complexes. Accordingly the formed CT complexes could be formulated as [(Res)(QL)], [(Res)(PA)], [(Res)(TCNQ)] and [(Res)(DDQ)]. It was found that the obtained CT complexes are nanoscale, semi-crystalline particles, thermally stable and formed through spontaneous reaction. The results obtained herein are satisfactory for estimation of drug Res in the pharmaceutical form.

Introduction

Considerable attention has recently been devoted to the formation of stable charge-transfer (CT) complexes that result from the reaction between acceptors and drugs or biological compounds. This interest stems from the significant physical and chemical properties of these complexes. The CT complexation is an important technique that is cheaper, simpler, and more efficient than the methods of drug determination described in the literature [1]. The study of the CT complexes of drugs may be useful in understanding the drug–receptor interactions and the mechanism of

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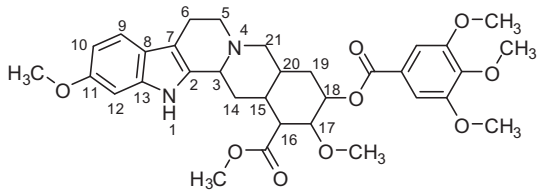

Scheme 1. Chemical structure of reserpine.

drug action [2–4]. Furthermore, the crystalline CT complexes have a vital role in biological systems such as antimicrobial activity and DNA-binding. Literature shows that the CT complexes exhibit potential antimicrobial properties against Gram-positive and Gram-negative bacteria as well as fungi [5–10].

Herein, the CT interaction between the drug reserpine and four acceptors are investigated. Reserpine (Res; $C_{33}H_{40}N_2O_9$, Scheme 1) is an indole alkaloid antipsychotic and antihypertensive that exists at room temperature as a white or pale-buff to yellow odorless powder [11]. It is practically insoluble in water; freely soluble in chloroform, methylene chloride, and glacial acetic acid; soluble in benzene and ethyl acetate; and slightly soluble in methanol, ethanol, acetone, ether, and weak solutions of acetic and citric acids. It is stable under normal storage conditions but is subject to oxidation and hydrolysis. Res acquire a yellow color with pronounced fluorescence, especially after addition of acid or exposure to light. When heated to decomposition, it emits toxic fumes of nitrogen oxides [12]. Res is a biologically active naturally occurring drug produced by several members of the genus *Rauwolfia*, a climbing shrub indigenous to southern and Southeast Asia. Extracts of *Rauwolfia serpentine* have been used medicinally in ancient India for centuries. In traditional Hindu medicine, the roots of *Rauwolfia* serpentine was brewed as a tea and were used in humans to treat hypertension, insanity, fever, snakebite, insomnia and cholera. The purified alkaloid, reserpine, was isolated in 1952 from the died root of *Rauwolfia serpentine* and is considered the first modern drug for the treatment of hypertension [13]. Drug Res is now largely used to lower blood pressure, reduce the heart rate, relief of psychotic symptoms and as a tranquilizer and sedative in humans [14–17]. It has also been used as a radioprotective agent and experimentally as a contraceptive [18,19].

To provide basic data that can be used to understand of drug–receptor mechanism, the CT complexes of Res with quinol (QL), picric acid (PA), tetracyanoquinodimethane (TCNQ) and dichlorodicyanobenzoquinone (DDQ) were synthesized and spectroscopically investigated. The newly synthesized CT complexes have been structurally characterized via elemental analysis; infrared (IR), Raman, ^{1}H NMR and electronic absorption spectroscopy; powder X-ray diffraction; and scanning electron microscopy (SEM) to interpret the behavior of the interactions. The spectroscopic and physical data were analyzed in terms of formation constant (K_{CT}), molar extinction coefficient (ε_{CT}), standard free energy (ΔG°), oscillator strength (f), transition dipole moment (μ), resonance energy (R_N) and ionization potential (I_D). The thermal behavior of the obtained complexes and the kinetic and thermodynamic parameters (E^*, A, ΔS^*, ΔH^* and ΔG^*) have also been investigated.

Experimental

Chemicals

All chemical used were of high grade. Reserpine (Res; Methyl (3β, 6β, 17α, 18β, 20α)-11,17-dimethoxy-18-[(3,4,5-trimethoxybenz oyl) oxy]yohimban-16-carbox-ylate, $C_{33}H_{40}N_2O_9$) and π-acceptors of quinol (QL), picric acid (PA), 7,7′,8,8′-tetracyanoquinodimethane (TCNQ) or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) were purchased from Merck Chemical Company and were used without further purification. Commercially available spectroscopic grade solvents (BDH) were also used as received.

Instrumental measurements

The elemental analyses of the carbon and hydrogen contents were performed by the microanalysis facility at Cairo University, Egypt, using a Perkin–Elmer CHN 2400 (USA). The electronic absorption spectra of methanolic solutions of the donor, acceptors and resulting CT complexes were recorded over a wavelength range of 200–800 nm using a Perkin–Elmer Lambda 25 UV/Vis double-beam spectrophotometer at Taif University, Saudi Arabia. The instrument was equipped with a quartz cell with a 1.0 cm path length. The mid-infrared (IR) spectra (KBr discs) within the range of 4000–400 cm^{-1} for the solid CT complexes were recorded on a Shimadzu FT-IR spectrophotometer with 30 scans at 2 cm^{-1} resolution. The Raman laser spectra of the samples were measured on a Bruker FT-Raman spectrophotometer equipped with a 50 mW laser at Taif University, Saudi Arabia. ^{1}H NMR spectra were collected by the Analytical Center at King Abdul Aziz University, Saudi Arabia, on a Bruker DRX-250 spectrometer operating at 250.13 MHz with a dual 5 mm probe head. The measurements were performed at ambient temperature using DMSO-d_6 (dimethylsulfoxide, d_6) as a solvent and TMS (tetramethylsilane) as an internal reference. The ^{1}H NMR data are expressed in parts per million (ppm) and are internally referenced to the residual proton impurity in the DMSO solvent. Thermogravimetric analysis (TGA) was performed under an air atmosphere between room temperature and 800 °C at a heating rate of 10 °C/min using a Shimadzu TGA-50H thermal analyzer at the Central Lab at Ain Shams University, Egypt. The X-ray diffraction patterns for the obtained CT complexes were collected on a PANalytical X'Pert PRO X-ray powder diffractometer at the Central Lab at Ain Shams University, Egypt. The instrument was equipped with a Ge(III) monochromator, and a Cu Kα_1 X-ray source with a wavelength of 0.154056 nm was used. Scanning electron microscopy (SEM) images were collected on a Jeol JSM-6390 instrument at Taif University, Saudi Arabia. The instrument was operated at an accelerating voltage of 20 kV.

Procedures

Reaction procedure

The solid CT complexes of Res with QL, PA, TCNQ or DDQ were prepared by mixing equimolar amounts of Res with each acceptor in methanol (10 ml). The solutions were stirred for about 20 min, and allowed to evaporate slowly at room temperature, which resulted in the precipitation of the solid CT complexes. The resultant complexes were filtered off, washed well with little amounts of methanol, and then collected and dried under vacuum over anhydrous calcium chloride for 24 h. Elemental analyses (C and H) of the Res CT complexes were performed, and the obtained results are as follows: [(Res)(QL)]; $C_{39}H_{46}N_2O_{11}$; Mol. wt. = 718.79; Dark brown; Calc.:%C, 65.11;%H, 6.40; Found:%C, 64.89;%H, 6.38. [(Res)(PA)]; $C_{39}H_{43}N_5O_{16}$; Mol. wt. = 837.78; Yellow; Calc.:%C, 55. 86;%H, 5.13; Found:%C, 55.71;%H, 4.96. [(Res)(TCNQ)]; $C_{45}H_{44}N_6$ O_9; Mol. wt. = 812.87; Dark red; Calc.:%C, 66.43;%H, 5.41; Found: %C, 66.73;%H, 5.29. [(Res)(DDQ)]; $C_{41}H_{40}Cl_2N_4O_{11}$; Mol. wt. = 835. 68; Dark brown; Calc.:%C, 58.87;%H, 4.79; Found:%C, 58.50;%H, 4.91.

Preparation of standard stock solutions of the donor and acceptors

Stock solutions of the Res and acceptors at a concentration of 5.0×10^{-3} M were freshly prepared before each series of measurements by dissolving precisely weighed amounts in the appropriate volume of the methanol solvent. The stock solutions were protected from light.