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Spectroscopic and thermodynamic study of charge transfer complexes of cloxacillin sodium in aqueous ethanol medium

Dalim Kumar Roy[a], Avijit Saha[b], Asok K. Mukherjee[b,*]

[a] *Allen Laboratories Ltd., Allen Estate, Krishnapur Road, Kolkata 700102, India*
[b] *Department of Chemistry, The University of Burdwan, Golapbag, Burdwan 713104, India*

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Abstract

Cloxacillin sodium has been shown to form charge transfer (CT) complexes of 1:1 stoichiometry with a number of electron acceptors in 50% (v/v) aqueous ethanol medium. From the trends in the CT absorption bands, the vertical ionization potential of the drug molecule (cloxacillin sodium) has been estimated to be 7.89 eV. The enthalpies and entropies of formation of two such complexes have been determined by estimating the formation constants spectrophotometrically at five different temperatures. The oscillator strengths and transition dipole moments of these complexes have been determined. It has further been noted that the reduction of *o*-chloranil by aqueous ethanol is completely inhibited by cloxacillin sodium, a phenomenon that makes the present study of formation equilibrium possible.

Keywords: Charge transfer complexes; Cloxacillin sodium; Aqueous ethanol

1. Introduction

Study of the physicochemical properties of drug molecules in solution is of importance in pharmacokinetics and is being recently carried out [1]. Development of methods of analysis of small quantities of these drugs in meat and milk of animals administered with such drugs is another important purpose of studying the physicochemical properties of the drugs in vitro [2]. Most of such methods involve HPLC or GC techniques [3–5]. Spectroscopic and thermodynamic methods, on the other hand, should be useful not only for detection and quantification of these drugs in a given sample of tissue/blood, but also for understanding the mechanism of binding of the drug molecules to other substances present in living systems. The possible role of electron donor–acceptor complexes in drug–receptor binding was indicated much earlier by Webb and Thompson [6]. The electron donor ability of a drug molecule, which can be directly measured from its vertical ionization potential, is an important parameter in this respect. This parameter can be determined through the study of charge transfer (CT) complexes as has been shown in a recent study with paracetamol [7]. CT complexation is also an important phenomenon in biochemical and bioelectrochemical energy transfer processes [8–17]. Not only this, CT complexes of a drug molecule may absorb in the visible range and thus lead to easy detection and estimation of the drug. Moreover, the formation constant of a drug–protein complex (commonly called drug–protein association constant by pharmacokineticists) is an important parameter in the context of targeted drug delivery [18,19]. For this purpose we have carried out a detailed spectroscopic and thermodynamic study of CT complexation of the antibacterial drug, sodium (6*R*)-6-[3-(2-chlorophenyl)-5-methylisoxazole-4-carboxamido] penicillanate, which is commonly known as 'cloxacillin sodium' (Fig. 1). This drug is known to bind to human serum albumin [20]. With a nitrogen-containing heterocyclic ring, it is a potential electron donor. On the other hand, quinones are well-known electron acceptors [21]. So there is a possibility of CT complex formation of cloxacillin sodium with quinones. In particular, menadione, i.e., 2-methyl-1,4-napthoquinone, is a vitamin

* Corresponding author. Tel.: +91 342 2558545; fax: +91 342 2560810.
E-mail address: akm_13@rediffmail.com (A.K. Mukherjee).

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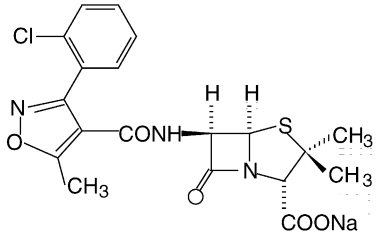

Fig. 1. Structure of sodium (6*R*)-6-[3-(2-chlorophenyl)-5-methylisoxazole-4-carboxamido] penicillanate (cloxacillin sodium).

molecule (Vitamin K_3). The study, therefore, is expected to have some relevance in pharmacology.

2. Experimental

Menadione (i.e., 2-methyl-1,4-napthoquinone), 2,3-dichloro-1,4-napthoquinone and the drug cloxacillin sodium from Sigma and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) from Aldrich, were used without further purification. The other chemicals, *o*-chloranil (i.e., 3,4,5,6-tetrachloro-1,2-benzoquinone) from Sigma and *p*-chloranil (i.e., 2,3,5,6-tetrachloro-1,4-benzoquinone) from Fluka, Switzerland, were further purified by sublimation just before use. The solvent, ethanol was purified by the method described in [22,23] as follows: commercial grade absolute alcohol was dried over lime and distilled. The distillate was refluxed for half an hour with iodine-activated magnesium and then distilled under moisture-free conditions. The entire experiment was done in a medium containing 50% (v/v) of conductivity water and 50% of the purified ethanol. Such a medium was chosen because cloxacillin sodium is soluble in water but insoluble in ethanol while the acceptors used are soluble in ethanol but insoluble in water. Moreover, such a medium is closer to biological system than non-polar solvents which are generally used in the study of charge transfer complexes. All optical measurements were done on a UV 1601 PC model Simadzu spectrophotometer fitted with a Peltier controlled thermobath.

3. Results and discussion

3.1. Observation of CT bands

In the present study, CT bands were observed in case of complexes of cloxacillin sodium (Fig. 1) with: (i) *o*-chloranil; (ii) *p*-chloranil; (iii) menadione; (iv) DDQ; and (v) 2,3-dichloro-1,4-napthoquinone. In 50% aqueous ethanol medium, the spectrum of cloxacillin sodium itself is peaked at 341 nm and it does not absorb beyond 380 nm as shown in Fig. 2. To obtain CT bands of the drug–quinone complexes, spectrum of each of the solutions (in 50% ethanol) containing cloxacillin sodium as donor and the acceptors (i)–(v) separately was recorded against the pristine acceptor solution as

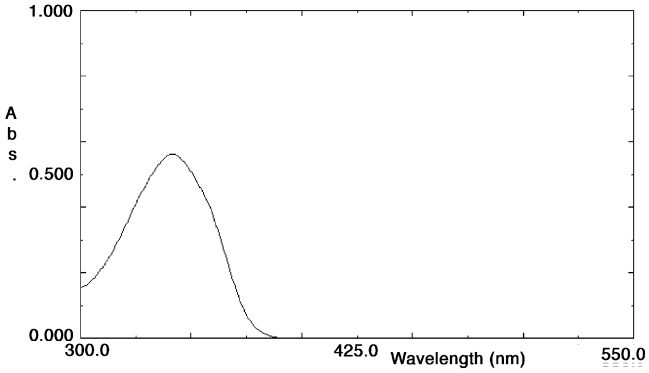

Fig. 2. Absorption spectrum of cloxacillin sodium (1.275×10^{-2} mol dm^{-3}) against the solvent (50% ethanol–water (v/v)) as reference. In the ordinate, 'Abs.' means 'absorbance'.

reference. The CT bands in solution were detected by taking high concentration of the donor, viz. [cloxacillin sodium] $\approx 10^{-2}$ mol dm^{-3} compared to that of each acceptor ($\approx 10^{-3}$ to 10^{-4} mol dm^{-3}). CT absorption bands for four typical cases under study are shown in Fig. 3. As evident from Fig. 2, the absorption due to free cloxacillin does not interfere with the CT bands. Two important points must be mentioned here: (a) *o*-Chloranil undergoes slow reduction by aqueous ethanol as was observed by the gradual spectral change of the aqueous ethanolic solution with time. But this reduction was completely inhibited in the presence of cloxacillin sodium, and this fact makes the present study of formation equilibrium of the drug–*o*-chloranil complex possible. (b) 2,3-Dichloro-1,4-napthoquinone slowly reacts with cloxacillin sodium in aqueous ethanolic medium; the wavelength (λ_{CT}) of the CT absorption peak remains unchanged but the intensity of the absorption gradually changes with time. For this reason, we have used only the λ_{CT} for analysis but have not carried out formation equilibrium study of this complex in present work. The vertical electron affinities (E_A^v) of the acceptors (i)–(iv) were collected from literature [21,24,25] and that of the fifth

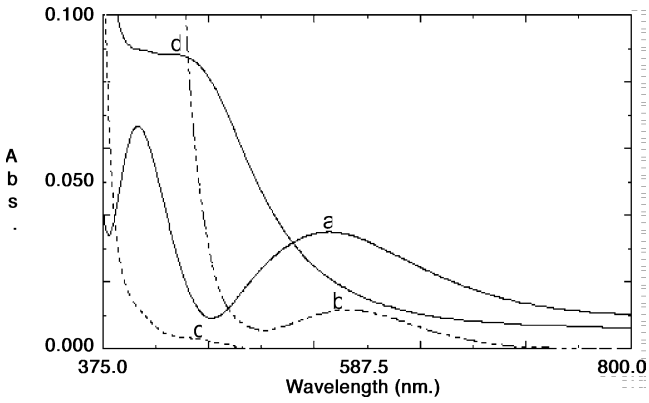

Fig. 3. CT absorption spectra of mixtures containing cloxacillin sodium (10^{-2} mol dm^{-3}) and (a) *o*-chloranil (10^{-4} mol dm^{-3}), (b) DDQ (10^{-4} mol dm^{-3}), (c) menadione (10^{-3} mol dm^{-3}) and (d) 2,3-dichloro-1,4-napthoquinone (10^{-3} mol dm^{-3}) against the pristine acceptor solutions as reference. In the ordinate, 'Abs.' means 'absorbance'.