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Structural considerations on acridine/acridinium derivatives: Synthesis, crystal structure, Hirshfeld surface analysis and computational studies

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ABSTRACT

This article describes a detailed study of the molecular packing and intermolecular interactions in crystals of four derivatives of acridine, i.e. 9-methyl-, 9-ethyl, 9-bromomethyl- and 9-piperidineacridine (**1**, **2**, **3** and **4**, respectively) and three 10-methylacridinium salts containing the trifluoromethanesulphonate anion and 9-vinyl-, 9-bromomethyl, and 9-phenyl-10-methylacridinium cations (**5**, **6** and **7**, respectively). The crystal structures of all of the compounds are stabilized by long-range electrostatic interactions, as well as by a network of short-range C–H···O (in hydrates and salts **3** and **5**–**7**, respectively), C–H···π, π–π, C–F···π and S–O···π (in salts **5**–**7**) interactions. Hirshfeld surface analysis shows that various intermolecular contacts play an important role in the crystal packing, graphically exhibiting the differences in spatial arrangements of the acridine/acridinium derivatives under scrutiny here. Additionally, computational methods have been used to compare the intermolecular interactions in the crystal structures of the investigated compounds. Computations have confirmed the great contribution of dispersive interactions for crystal lattice stability in the case of 9-substituted acridine and electrostatic interactions for the crystal lattice stability in the case of 9-substituted 10-methylacridinium trifluoromethanesulphonates. The value of crystal lattice energy and the electrostatic contribution in the crystal lattice energy of monohydrated acridine derivatives have confirmed that these compounds have behave as acridinium derivatives.

1. Introduction

Natural and synthetic acridine derivatives are among the oldest classes of bioactive agents. These compounds exhibit fungicidal, antimicrobial, anti-parasitic, anti-inflammatory, anticancer and antiviral activities [1–4]. Their anti-proliferative properties have been reported as well. Some acridine derivatives can bind DNA through intercalation [1], which leads to cell apoptosis. In addition, acridine-based derivatives have been studied as anticancer agents, which are believed to express their activity through the binding of DNA [2,5]. Similarly, 10-substituted acridinium derivatives, with a rigid aromatic tricyclic ring system, have been shown to possess potent chemo-sensitization pharmacophores [6].

On the other hand, an interesting group of acridine derivatives are those capable of chemiluminescence. This property is displayed by acridinium cations alkyl-substituted at the endocyclic nitrogen atom and containing electron-attracting substituents at C9. This latter atom is thus susceptible to the attack of anionic oxidants, e.g. hydrogen peroxide and persulphates [7–13]. Oxidation gives rise to electronically excited N-alkyl-9-acridinones; their relaxation is accompanied by the emission of light, i.e. chemiluminescence [7,8,10,11]. The efficiency of chemiluminescence, no greater than a few per cent [7,11], can be affected by the presence of various substances in the medium, including nucleophilic species, competing with oxidants for substitution at C9 [7,8,14]. This effect is utilized in the assay of oxidants, nucleophiles or other entities, and in such cases acridinium cations serve as chemiluminogenic indicators [7,9,14]. Acridinium chemiluminogens can also be linked by a spacer (e.g. an alkyl chain) to an active group capable of reacting with appropriate fragments of macromolecules. Such chemiluminescent labels are widely used in chemical, medical, biological and environmental analyses [7–9,12].

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We investigated the crystal structure as well as the intra- and intermolecular interactions of 10-methyl-9-phenoxycarbonylacridinium derivatives [14–19] and 10-methyl-9-cyanoacridinium cations [20]. A disadvantage of these acridinium derivatives is the relatively inefficiency of their chemiluminescence. This encouraged us to search for new acridinium-based derivatives capable of reacting more efficiently with oxidizing agents to produce light. 9-Alkylacridine is the precursor of the 10-methyl-9-alkylacridinium cation, which displays a promising chemiluminogenic ability [21,22].

Intermolecular interactions, such as hydrogen bonds and π–π interactions, are of fundamental importance for supramolecular assembly and consequently for the properties of organic and inorganic compounds [23–25]. Self-assembly and molecular recognition processes of the compounds play a significant role in the context of their use as technological materials, drugs, or biologically active molecules [26–29]. Strong (O–H···O and N–H···O) and weak (C–H···O) hydrogen bonding [30–35] remains the most reliable and widely used means of enforcing molecular recognition of crystalline materials. On the other hand, other weaker forces (π–π interactions) [29,32,36–39] have also been successfully utilized for such purposes. The increased interest in the understanding of the geometry, energies and nature of hydrogen bonding [30–35] and π–π interactions [29,32,36–39] in the past two decades, expressed primarily by the increasing number of publications on this topic, is understandable, given the enormous importance of these forces in building supramolecular self-assemblies.

In this paper, we report the results of the X-ray crystal structure determination of seven new 9-substituted acridine derivatives and 9-substituted-10-methylacridinium trifluoromethanesulphonates (Scheme 1). A comparative characterization of the title compounds is carried out, and details regarding the structural differences between them are discussed in the context of the intermolecular interactions present in the crystal state. In addition, intermolecular non-covalent interactions were studied using the Hirshfeld surface analysis [40–42]. In order to understand the nature of intra- and intermolecular interactions, we applied computational methods (CRYSTAL09 program at the DFT level of theory). The latter approach, the crystal lattice energies (E_L), together with the electrostatic (E_C) and dispersive contribution ($E(D^*)$) to the crystal lattice energy, and basis set superposition error energy correction (E_{BSSE}) were calculated and interpreted.

2. Materials and methods

2.1. Synthesis

The chemicals were purchased from Sigma–Aldrich unless indicated otherwise. The purity of the compounds was checked by HPLC (Waters 600 E Multisolvent Delivery System, Waters 2487 Dual λ Absorbance Detector; mobile phase: acetonitrile/water = 70%/30% supplemented with 0.1% of TFA; stationary phase: C-8 column, 3 × 150 mm, 'Symmetry') (the relative areas under the main signal were >99% in all cases) and their identity confirmed by mass spectrometry. The compounds obtained were subjected to elemental analyses (EAGER 200, Carlo Erba Instruments) and TLC tests in the above-mentioned system. ^{1}H spectra were recorded at room temperature on a Bruker AVANCE III 500 MHz.

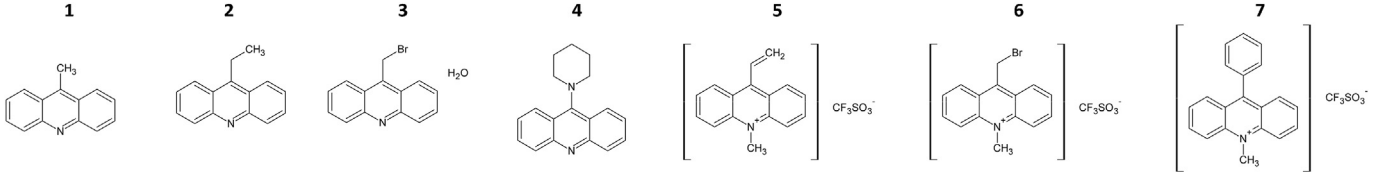
9-Methylacridine (**1**). A mixture of 10 g of diphenylamine (59.1 mmol), acetic acid (10.0 ml), and anhydrous zinc chloride (40.0 g, 293.5 mmol) was heated at 220 °C for 17 h. The reaction mixture was digested with hot 10% aqueous sulphuric acid and then strongly alkalified with concentrated aqueous ammonia to dissolve the zinc chloride. The insoluble residue was extracted with toluene. The organic phase was washed with water (100 mL) and dried over sodium sulphate. After evaporation of the solvent, the crude product was purified by column chromatography (eluent *n*-hexane/ethyl acetate = 5/1 v/v). Yield 81%; m.p. = 391 K; the % of elements found/calculated, C 86.93/87.01, H 5.74/5.74, N 7.09/7.25; ^{1}H NMR (CD_3CN), δ, ppm (J, Hz): 3.06 (3H, s); 7.52 (2H, t, J = 7.5); 7.71 (2H, t, J = 7.4); 8.04 (2H, d, J = 8.6); 8.28 (2H, d, J = 8.8).

9-Ethylacridine (**2**). A mixture of 0.17 g of diphenylamine (1 mmol), 1.1 ml propionic acid (15 mmol) and 0.46 g zinc chloride (3 mmol) was stirred and microwave-irradiated at 110 °C and 120 W for 2 h. The mixture was diluted with dichloromethane, washed with water, diluted with sodium hydroxide, washed again with water and dried over magnesium sulphate. After evaporation of the solvent, the crude product was purified by column chromatography (eluent 1–3% 2-propanol in chloroform). Yield 87%; m.p. = 387 K; the % of elements found/calculated, C 86.69/86.92, H 6.34/6.32, N 6.71/6.76; ^{1}H NMR ($CDCl_3$), δ, ppm (J, Hz): 1.47 (3H, t, J = 7.7); 3.65 (2H, q, J = 7.7); 7.56 (2H, t, J = 7.7); 7.77 (2H, t, J = 8.0); 8.26 (4H, d, J = 8.8).

9-Bromomethylacridine (**3**) was synthesized according to the procedure described in Ref. [43]. Yield 77%; m.p. = 443 K; the % of elements found/calculated, C 61.26/61.79, H 3.64/3.70, N 5.03/5.15; ^{1}H NMR ($CDCl_3$), δ, ppm (J, Hz): 5.38 (2H, s); 7.62 (2H, t, J = 7.7); 7.78 (2H, t, J = 7.7); 8.31 (4H, d, J = 8.8).

9-Piperidylacridine (**4**). 0.213 g (1.0 mmol) of 9-chloroacridine hydrochloride was dissolved in 2 ml piperidine and heated to 90 °C with constant stirring for 6 h. The solvent was evaporated under vacuum at 50 °C. The residue was washed with aqueous methanol and dried in a vacuum. Yield 91%; m.p. = 383 K; the % of elements found/calculated, C 81.96/82.41, H 7.01/6.92, N 10.93/10.68; ^{1}H NMR ($CDCl_3$), δ, ppm (J, Hz): 1.80 (2H, m); 1.84 (4H, m); 3.59 (4H, m); 7.38 (2H, t, J = 7.6); 7.64 (2H, t, J = 7.6); 8.15 (2H, d, J = 8.6); 8.28 (2H, d, J = 8.9).

General procedure for the synthesis of 10-methylacridinium trifluoromethanesulphonate derivatives To a solution of 1 mmol of an acridine derivative in 10 ml dry dichloromethane were added 4 mmol 2,6-di*tert*-butylpyridine and 5 mmol methyl trifluoromethanesulphonate. The solution was stirred at room temperature for 3 h. The precipitate was filtered off and washed with dichloromethane. The filtrate was evaporated under vacuum at room temperature to 5 ml and diluted with diethyl ether. The



Scheme 1. Canonical structures of the compounds investigated; **1** – 9-methylacridine, **2** – 9-ethylacridine, **3** – 9-(bromomethyl)acridine monohydrate, **4** – 9-piperidin-1-ylacridine, **5**–10-methyl-9-vinylacridinium trifluoromethanosulphonate, **6** – 9-(bromomethyl)-10-methylacridinium trifluoromethanosulphonate, **7**–10-methyl-9-phenyl-acridinium trifluoromethanesulphonate.