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Novel Heterocyclic Schiff Base, (*Z*)-4-((2-((2-Aminophenyl)disulfanyl)phenylimino) (Phenyl)Methyl)-3-Methyl-1-Phenyl-1H-Pyrazol-5-ol Crystals for Enzymatic Studies

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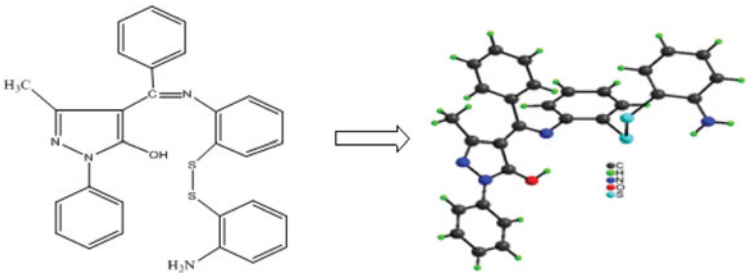
Graphical Abstract



A new dithio Schiff base was synthesized and characterized by spectroscopic (FT-IR, UV-Vis, H^1-NMR, and C^{13}-NMR) and X-ray diffraction studies. Molecular interactions (inter and intra) between the neutral entities are discussed.

Schiff base ligand, (Z)*-4-((2-((2-aminophenyl)disulfanyl)phenylimino)(phenyl) methyl)-3-methyl-1-phenyl-1H-pyrazol-5-ol (**1**), was synthesized by the reaction between 2-phenyl-4-benzoyl-5-methyl-pyrazolin-3-one and 2-amino thio phenol (1:2 molar ratio). The structural elucidation was done by spectroscopic (FT-IR, UV-Vis, H^1-NMR, C^{13}-NMR) and X-ray diffraction studies. Single crystal X-ray diffraction studies revealed that **1** has monoclinic system with space group P21/c with* a = *15.654 (4) Å,* b = *12.848 (4) Å,* c = *14.219 (4) Å;* $\alpha = 90°$, $\beta = 113.65\ (6)°$, $\gamma = 90°$, *and* Z = *4. The possible intramolecular (C-H···N) and intermolecular (C-H···O, C-H···S, N-H···O) interactions of **1** were also been discussed.*

Keywords Molecular interactions; pyrazole derivatives; Schiff base; X-ray diffraction studies

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1. Introduction

The chemistry of pyrazolone derivatives has attracted much attention because of their interesting structural properties and applications in diverse areas [1–4]. Pyrazolone derivatives are useful reagents for the extraction and separation of various metal ions [5,6]. Pyrazolone derivatives can also be used as NMR shift reagents, in laser materials, in chromatographic study and in the petrochemical industries [7,8]. Many of pyrazolone derivative ligands exists in three tautomeric forms viz., keto-amine, keto-imine, and imine-ol. Because of the tautomerism, they show interesting structural and spectroscopic properties which have been the focus of many reports [9,10]. Pyrazolone derivatives are also used as starting materials for the synthesis of biologically active compounds and for the construction of condensed heterocyclic systems [11]. Among pyrazolone derivative ligands, acyl pyrazolones have been studied extensively owing to their effective properties with respect to extracting metal ions [12]. Pyrazolyl and their derived ligands can form relevant coordination compounds with different metal ions. Recently, few Schiff bases were prepared by the reaction between 3-methyl-1-(4′-methylphenyl)-2-pyrazoline-5-one and aromatic amines [13].

Sulfur is one of the essential elements for life, and is widely used in biochemical processes. Sulfur in organosulfur compounds expected to have similarities with carbon-oxygen, carbon-selenium, and carbon-tellurium compounds, which is true to some extent. Two of the 20 common amino acids are organosulfur compounds; antibiotics penicillin and sulfa drugs both contain sulfur. The thiol group plays a very important role in biology. When the thiol groups of two cysteine residues are brought near to each other in the course of protein folding, an oxidation reaction can generate a cysteine unit with a disulfide bond(-S-S-) [14]. Disulfide bonds can contribute to a protein's tertiary structure, if the cysteines

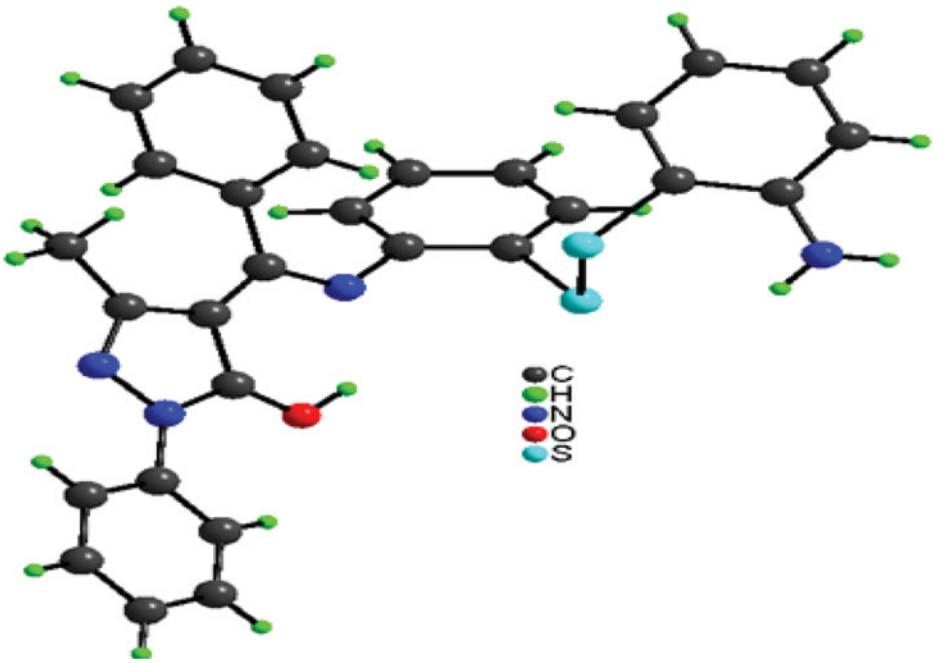


Figure 1. Molecular structure view of the new Schiff base **1**.

Table 1. Crystallographic data and refinement details of **1**

Empirical formula	$C_{29}H_{24}N_4OS_2$
Formula weight	508.66
Temperature (K)	273
Wavelength (Å)	0.71073
Space group	P21/*c*
Unit cell dimensions	
a (Å)	15.654 (4)
b (Å)	12.848 (4)
c (Å)	14.219 (4)
α (^{0})	90
β (^{0})	113.65
γ (^{0})	90
Cell volume (A^3)	2619.7 (13)
Z	4
Absorption coefficient (mm^{-1})	0.233
*F*000	1064
Crystal size	$0.39 \times 0.20 \times 0.12$
Crystal color	Yellow
Crystal description	Needle
Θ range for data collection (^{0})	1.42—24.00
Reflections (collected/unique)	4104/2945
Goodness-of-fit	1.233
R indices [$1 > 2\sigma(I)$]	$R1 = 0.1220$, $wR_2 = 0.2128$
R indices (all data)	$R_1 = 0.1668$, $wR_2 = 0.2327$

are part of the same peptide chain, or contribute to the quaternary structure of multi-unit proteins by forming fairly strong covalent bonds between different peptide chains. Sulfhydryl groups in the active site of an enzyme can form non-covalent bonds with the enzyme's substrate as well, contributing to catalytic activity.

By keeping the above points in view, herein, we report the synthesis, spectral properties, crystal structure and the possible molecular interactions of (*Z*)-4-((2-((2-imino phenyl)disulfanyl)phenyl)imino)(phenyl)methyl)-3-methyl-1-phenyl-1H-pyrazol-5-ol which bearing a disulfide bond.

Table 2. Summary of bond distance of various types of weak interactions of **1**

Weak interactions	Bond distance (Å)
CH···N intra molecular	2.293(11),2.437(7)
CH···O intermolecular	3.172(5),3.153(6),3.141(5)
N-H···O	2.243(7)
C-H···S	2.933(2)

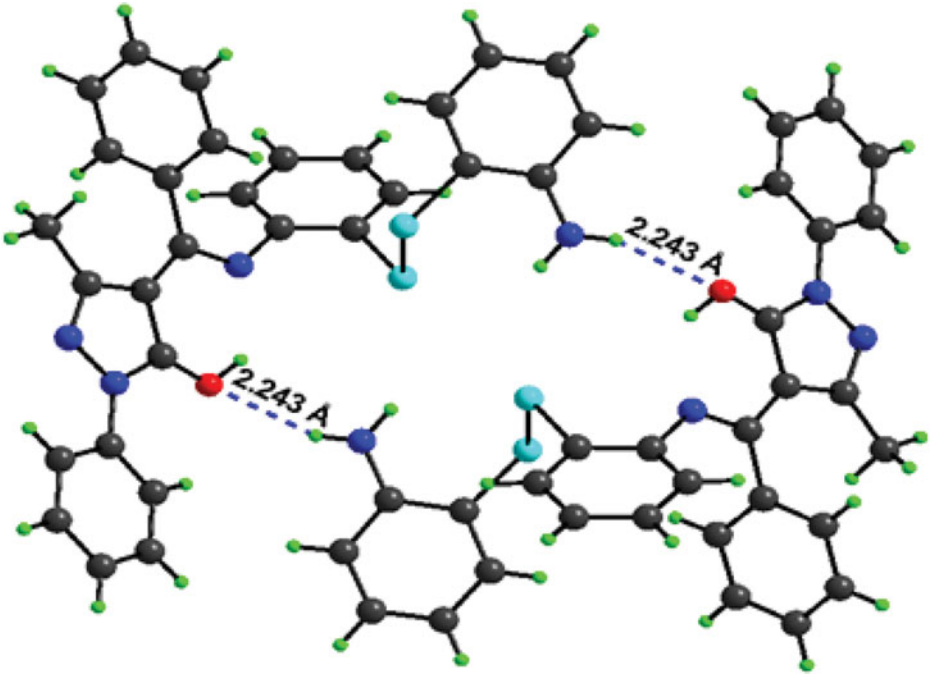


Figure 2. Intermolecular interactions of **1** showing NH···O (blue dotted) interactions leads to dimer formation. Color code: C, grey; H, green; N, blue; O, red; S, sky blue. (For interpretation of the references to colors in this figure legend, the reader is referred to the web version of the article).

2. Experimental

2.1. Physical Methods

All chemicals were purchased from commercial sources and used as such. Infrared spectrum was recorded on a Perkin Elmer spectrophotometer of RXI model. UV-Visible spectrum was recorded in dichloromethane solution on a Systronics-2202 double beam spectrophotometer. Elemental analyses were obtained from SAIF, Cochin, India. H^1- and C^{13}-NMR spectra were carried out at Madurai Kamaraj University, Madurai, India. X-ray diffraction studies were carried out at Indian Institute of Technology, New Delhi, India.

Fluorescent experiments were recorded on a Shimadzu RF-5301PC spectrofluorophotometer at 298 K. Stock solution of **1** was prepared in 100% DMSO. For the measurements, excitation was at 400 nm; emission was measured at 520 nm. For both excitation and emission slit widths were 5 nm.

The pyrazole derivative 2-phenyl-4-benzoyl-5-methyl pyrazolin-3-one was synthesized by the standard procedure cited in the literature [15].

2.2. X-Ray Diffraction Studies

A single crystal (dimensions of 0.39 × 0.20 × 0.12 mm^3) was chosen to determine the molecular structure of **1** by X-ray diffraction analysis. Diffraction data were collected from Bruker SMART'diffractometer [16] with graphite fine focus

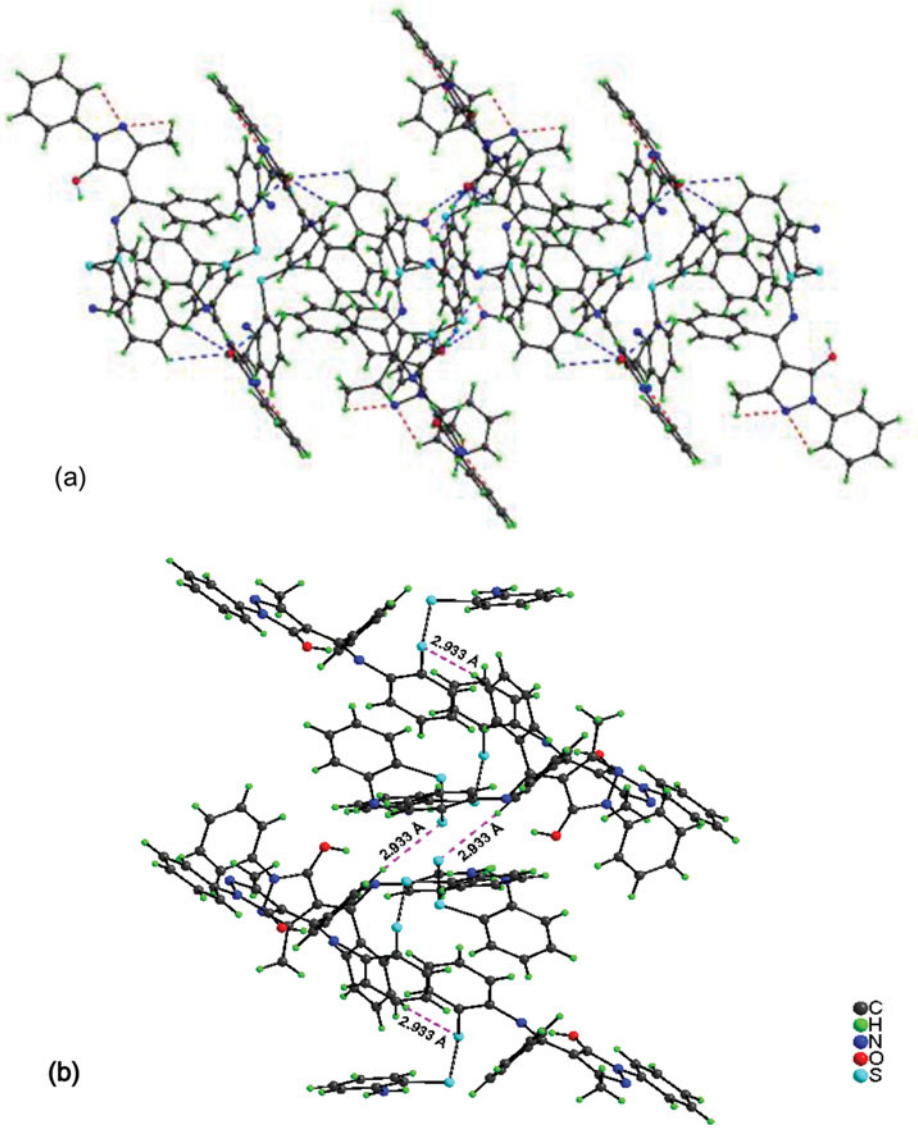


Figure 3. Intermolecular interactions of **1** showing (a) NH···O (red dotted) & CH···O (blue dotted) and (b) CH···S (pink dotted) interactions leads to 3-D network structure. Color code: C, grey; H, green; N, blue; O, red; S, sky blue. (For interpretation of the references to colors in this figure legend, the reader is referred to the web version of the article).

sealed tube. The structure was solved by Direct Methods. The programs SHELXS – 97 and SHELXL – 97 [17] were used for data collection, data reduction, and structure solution and structure refinement, respectively. Molecular graphics like ORTEP-3 was used for visualization. 327 parameters were refined with 4104 unique reflections.

2.3. Synthesis of Schiff Base (1)

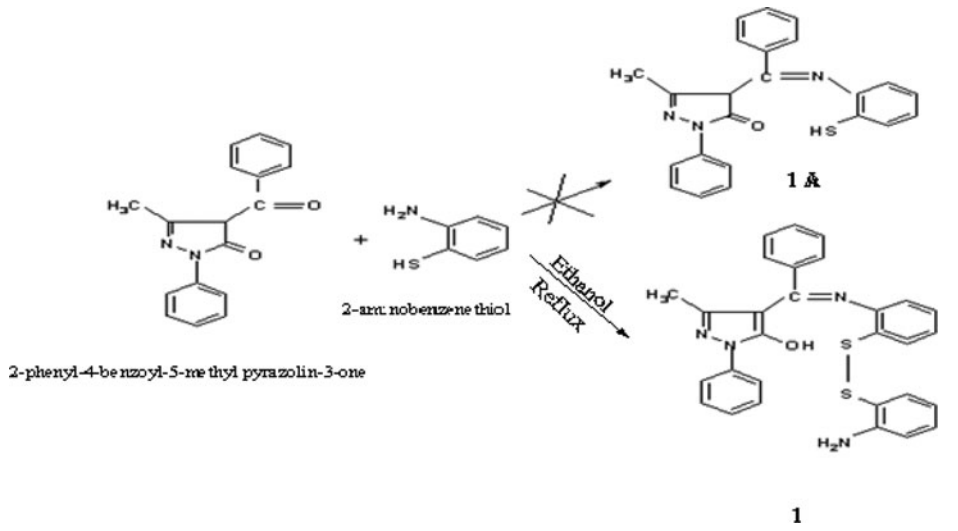
The Schiff base ligand was synthesized by refluxing ethanolic solution of mixture of 2-phenyl-4-benzoyl-5-methyl-pyrazolin-3-one (1.112 g; 4 mmol) and 2-amino thiophenol (1.2 ml, 8 mmol) for 3 h. The yellow precipitate was filtered-off and recrystallized twice from CH_3OH. The purity of the product was checked by thin layer chromatography. The yellow needle shaped crystals obtained were subjected to XRD and spectroscopic studies (Yield: 0.576 g (65%); m.pt. 276°C).

CHN analyzes for $C_{29}H_{24}N_4OS_2$% (found/calcd.): C: 68.37 (68.51); H: 4.74 (4.72); N: 11.08 (11.02); S: 12.52 (12.6); FT-IR (KBr, cm^{-1}):3455 (N-H stretching), 3059 (aromatic C-H stretching), 2918 (aliphatic C-H stretching), 1601 (azomethine C=N); UV-Vis (λ_{max}, nm): 262 ($n \rightarrow \pi^*$), 326 ($\pi \rightarrow \pi^*$); ^{1}H-NMR ($CDCl_3$, 300 MHz, ppm, δ): 12.8 (s, Ar-OH), 6.55-8.10 (m, ArH), 4.42 (bs, -NH_2), 1.59 (s, -CH_3); ^{13}C-NMR ($CDCl_3$, 75 MHz, ppm, δ): 165.75, 161.95, 148.37, 148.01, 138.89, 138.12, 135.54, 133.31, 131.97, 131.46, 131.20, 130.40, 128.73, 128.60, 128.55, 126.55, 126.21, 124.33, 119.17, 118.08, 117.66, 115.62, 102.37, 16.09.

3. Results and Discussion

Heterocyclic systems bearing the pyrazolyl moiety showed antibacterial, antifungal, anti-inflammatory and enzyme-inhibitory activities [18–21]. The possible weak interactions which bearing on the organized entities of higher complexity that result from the association of two or more chemical species held together by intermolecular forces are very important in the formulation of medicines. The type and strength of the interactions between the molecules in the formulations can affect the uptake of medication in the body. By keeping these points in view, with the help of X-ray diffraction analysis, the possible weak interactions of **1** were also studied.

The reaction of 2-phenyl-4-benzoyl-5-methyl-pyrazolin-3-one and 2-amino thiophenol in ethanol followed by filtration afforded **1** as needle shaped crystals (Scheme 1), and characterized on the basis of spectroscopic data and X-ray diffraction studies.



Scheme 1. Synthetic scheme of **1.**

3.1. Spectroscopic Studies

3.1.1. Infrared Spectroscopy. To elucidate the structure of the newly synthesized Schiff base, spectroscopic studies were carried out by using appropriate spectrometers. In IR spectra, a strong absorption band was observed at 3455 cm^{-1} which corresponds to N-H stretching, confirming the presence of NH_2 group in the Schiff base. The absorptions at 3059 and 2918 cm^{-1} are due to the presence of aromatic and aliphatic C-H stretching, respectively. The absorption at 1601 cm^{-1} indicates the presence of azomethine group which is a characteristic of Schiff base. The absence of S-H absorption band in the infrared region further concludes the absence of thiol group in the Schiff base ligand which ruled out the formation of **1A**. The presence of azomethine, amino group and the absence of thiol group lead to the assumption, the prepared Schiff base (**1**) is the unexpected one.

3.1.2. Absorption and Emission Spectroscopy. The UV-Vis spectra of **1** showed two absorption bands at 262 and 326 nm which are assigned to n $\rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transitions, respectively (Fig. S1). Elemental analyzes are in good agreement with the calculated value.

The fluorescence emission spectrum of **1** was obtained by an excitation at 400 nm (Fig. S2), which consist of a structured band (maximum of 520 nm). As expected, a broad excimeric emission appeared most likely resulting from an excited singlet-state fluorophore interacting with another in the ground state to form a fluorescent dimmer or an aggregate complex. Thus, it seems reasonable to assume that the formation of an intramolecular excimer occurs predominantly by nearest neighbor interaction resulting in higher aggregates.

3.1.3. Nuclear Magnetic Resonance (^1H &^{13}C) Spectroscopy. The ^{1}H-NMR spectra of **1** (Fig. S3) exhibit a singlet at δ 12.8 ppm for phenolic proton and a multiplet at δ 6.55–8.10 ppm for aromatic protons. Broad signal $\sim \delta$ 4.42 ppm indicates the presence of amino group; broadening of the peak is due to the quadrupole quenching. The singlet at δ 1.58 ppm indicates the presence of methyl protons. The comparison of the intensity of aromatic proton with methyl protons exactly confirms the presence of 14 numbers of aromatic protons. The absence of thiol (S-H) proton in ^{1}H-NMR concludes the formation of **1**.

In ^{13}C-NMR spectrum (Fig. S4), aromatic carbons shows cluster of peak in the range 116–168 ppm. The three different carbon atoms of pyrazole ring shows three distinct peaks at 128.73, 128.60, 128.55 ppm, respectively. Imine carbon is confirmed from the peak $\sim$ 104 ppm and the methyl carbon signal identified at 16 ppm.

3.2. X-Ray Diffraction Studies

The compound **1** crystallize in triclinic with space group P21/*c* (Fig. 1). Their crystallographic data are given in Table 1, whereas their important bond lengths are given in Table 2. The lattice parameters obtained are $a = 15.654$ (4) Å, $b = 12.848$ (4) Å, $c = 14.219$ (4) Å, $\alpha = 90^\circ$, $\beta = 113.65$ (6)°, $\gamma = 90^\circ$ and volume = 2619.7 (13) A^3. The intermolecular N-H···O (2.243(7)Å) interaction leads to the dimerization (Fig. 2) and intermolecular C-H···O (3.172(5), 3.153(6), 3.141(5)Å), CH···N (2.293(11), 2.437(7) Å) & C-H···S (2.933(2)Å) interactions show the way to 3-D network (Figs. 3(a) and (b)) were also predicted with the help of X-ray diffraction studies.

4. Conclusion

We have reported a novel Schiff base (**1**) as a new class of pyrazole derivative with disulphide bond (imine-ol form), which was accidently synthesized instead of keto-thiol tautomer. The single crystal X-ray diffraction analysis concludes **1** is the dithio Schiff base of pyrazole derivative. The XRD data confirms the presence of imine-ol tautomer of **1** in the solid state among the three possible tautomers. The spectroscopic characterization and X-ray diffraction results are well support the assigned molecular structure of **1**. Due to the short interatomic distances of **1**, the three possible weak interactions like NH···O, CH···O, and CH···S leads to 3D network. The presence of disulfide bond in **1** can be useful to carryout enzymatic studies. Interesting fluorescence emission spectrums ($\lambda_{max} = 520$ nm) make this heterocyclic compound (**1**), a candidate for identifying the protein folding. By using imine-ol tautomer of **1,** synthesis of various metal complexes and its evaluation of biological activities and identifying protein folding studies are ongoing project in our laboratory. The results will be published in due course.

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Supplementary Material

Copy of UV-Visible, Fluorescence and ^{1}H- & ^{13}C-NMR spectrum of **1** available in the supporting information. **CCDC – 838283** contain the supplementary crystallographic data for the title compound. Copies of the data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data centre, 12 Union Road, Cambridge CB2 1EZ, UK. fax: (+44)1223-336033; e-mail: deposit @ccdc.cam.ac.uk.

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