Ab initio structure determination of 3,4-diaminopyridin-1-ium dihydrogen phosphate

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The structure of 3,4-diaminopyridin-1-ium dihydrogen phosphate, $[C_5H_3(NH)(NH_2)_2]^+$ $(H_2PO_4)^-$, is solved from conventional X-ray powder diffraction data in direct space (monoclinic unit cell with $a = 16.0725(9)$ Å, $b = 7.3301(3)$ Å, $c = 14.6189(9)$ Å, $\beta = 96.869(1)°$, $V = 1803.2(2)$ Å^3, $Z = 8$, and space group $I2/c$), and optimized by energy minimization in the solid state. In the crystal structure of the title compound, dihydrogenphosphate tetrahedra are linked by strong hydrogen O-H…O bonds forming chains running parallel to the b-axis. Antiparallelly π–π stacked DAP cations form molecular columns in the spaces between the chains. Although the dominant interaction of the molecules with their surroundings is electrostatic, their bonding are further enhanced by N-H…O and C-H…O hydrogen bonds. © 2011 International Centre for Diffraction Data. [DOI: 10.1154/1.3660160]

Key words: 3,4-diaminopyridine, dihydrogen phosphate, Lambert-Eaton myasthenic syndrome, powder diffraction, crystal structure, *ab initio*, DFT

I. INTRODUCTION

The 3,4-diaminopyridine (3,4-DAP) molecule, whose crystal structure was recently established (Rubin-Preminger and Englert, 2007), can be used pharmaceutically (amifampridine) for the treatment of various diseases including the Lambert-Eaton myasthenic syndrome (LEMS) (McEvoy *et al.*, 1989). Tartrate and phosphate salts of 3,4-DAP were shown to have very high stability in storage conditions complying with international recommendations contrarily to 3,4-DAP (Guyon *et al.*, 2002). The 3,4-DAP phosphate (3,4-DAPP) formulation has obtained the orphan medicinal product status both in the European Union and in the Unites States (Quartel *et al.*, 2010).

The aim of the present work is to provide an answer for the 3,4-DAPP to the usual questions for pharmaceutical compounds: Is a single phase structure established by crystallographic investigation or are there polymorphs in the sample produced? Is there formation of a salt or cocrystallization of the API (active pharmaceutical ingredient) with H_3PO_4? In spite of the absence of a suitable single crystal, solving the structure of 3,4-DAPP is realized from powder diffraction data by using methodologies which continuously have demonstrated their efficiency during repeated blind tests (Le Bail *et al.*, 2009).

II. STRUCTURE DETERMINATION, RIETVELD REFINEMENTS, AND DFT STRUCTURE OPTIMIZATION

The powder diffraction pattern, recorded from a sample as received from the SERATEC Company (www.serateclab.com), could be indexed in a monoclinic cell by the MCMAILLE software (Le Bail, 2004). The FoMs (figures of merit) for the pattern selected for this study were found to be $M_{20} = 24.7$ (de Wolf, 1968), $F_{20} = 55.4$ (0.0049, 73) (Smith and Snyder, 1979), $McM_{20} = 362.0$ (Le Bail, 2008), and $Z = 8$. Using Le Bail fitting (Le Bail, 2005) for evaluating the reliability of the indexing and for intensities extraction, the $I2/c$ space group was determined unambiguously. The structure solution was done in the direct space using the ESPOIR software (Le Bail, 2001) moving in the unit cell, by a Monte Carlo process, a 3,4-diaminopyridine molecule and a PO_4 tetrahedron as rigid bodies (for a total of 12 degrees of freedom). This led to $R = 14\%$ on the first 100 "$|F_{obs}|$" extracted at low diffracting angles ($<42°2\theta$). Refinements were undertaken by the Rietveld (1969) FULLPROF software (Rodriguez-Carvajal, 1993). The hydrogen atom positions were suggested by the SHELXL software (Sheldrick, 2008) in the hypothesis of cocrystallization. By using soft restraints on N-C and C-C interatomic distances, the 3,4-diaminopyridine molecule was maintained in the shape similar to that established by Rubin-Preminger and Englert (2007). The O and P atoms of the H_3PO_4 group were refined freely, but all H atoms were fixed at their positions suggested by the procedure implemented in the SHELXL program.

Refined atomic coordinates were further optimized by energy minimization in the solid state using the VASP program (Kresse and Hafner, 1993; Kresse and Furthmüller, 1996a, 1996b). The electron exchange-correlation interaction was described in the generalized gradient approximation (Perdew and Wang, 1992). Plane waves formed the basis set, and calculations were performed using the projector-augmented wave method (Blöchl, 1994; Kresse and Joubert, 1999) and atomic pseudopotentials (Kresse and

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TABLE I. Experimental and Rietveld refinement details for the 3,4-diami-nopyridin-1-ium dihydrogen phosphate.

Diffractometer	Panalytical MPD PRO
Geometry	Bragg-Brentano
Goniometer	horizontal
Radiation type	Cu $K\alpha$
Wavelengths (Å)	1.54056, 1.54433
Detector	X′Celerator
Experimental range (°2θ)	5–70
Step size (2θ)	0.017°
Chemical formula	$C_5H_{10}N_3O_4P$
Space group	$I2/c$
Unit-cell parameter (Å or °)	
a	16.0725(9)
b	7.7301(3)
c	14.6189(9)
β	96.869(1)
Volume (Å³)	1803.2(2)
Z	8
No. contributing reflections	379
No. refined parameters	83 (total)
No. atomic coordinates parameters	39
No. restraints (C-C and C-N bonds)	8
No. isotropic thermal parameters	3
No. background parameters (interpolated from a set of points)	30
Profile shape	Pseudo-Voigt
η	0.525(8)
U	0.09
V	0.058(2)
W	0.0021(4)
Conventional Rietveld reliability factors	(Rietveld, 1969)
R_P (%)	9.46
R_{WP} (%)	8.23
R_{exp} (%)	5.46
R_B (%)	2.68
R_F (%)	5.61

Figure 2. (Color online) Atom numbering scheme for the moieties of 3,4-diaminopyridin-1-ium dihydrogen phosphate.

pyridinium cation. This new conformation was then confirmed by the independent calculations starting with a different initial geometry. The final formula of the title compound hence is $[C_5H_3(NH)(NH_2)_2]^+ (H_2PO_4)^-$. The same behavior conducting to a 3,4-pyridinium salt is observed when the phosphoric acid is replaced by succinic (Fun and Balasubramini, 2009), squaric (Koleva et al., 2007), or tartaric (Koleva et al., 2008) acids.

The basic crystallographic data, experimental, and Rietveld-refinement details are summarized in Table I. The Rietveld fit, atoms numbering, and crystal packing are depicted in Figures 1–3, respectively. The atomic coordinates obtained by both methods are listed in Table II, and the essential bond distances, bond angles are detailed in Table III. Hydrogen bonds geometry is summarized in Table IV, and X-ray powder diffraction data are given in Table V. Both sets of atomic coordinates were deposited (CIF) at the Crystallography Open Database (www.crystallography.net) (Gražulis et al., 2009) and in the supplementary date.

III. DISCUSSION

According to the optimized atomic coordinates, the molecule of 3,4-DAP$^+$ is essentially planar with the maximum

Hafner, 1994). The energy cut-off controlling the accuracy of the calculation was set to 500 eV, representing an extended basis set and consequently highly accurate calculations. The positions of all atoms were optimized by means of the conjugated gradient method in the Γ-point of the Brillouin zone with the unit-cell parameters fixed. In the course of the calculation, one of the hydrogen atoms from the H_3PO_4 group jumped to the molecule ring N atom forming
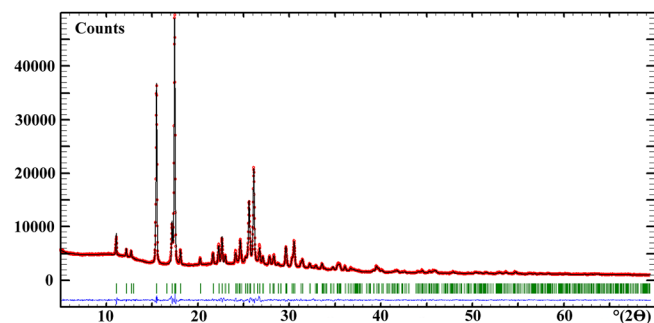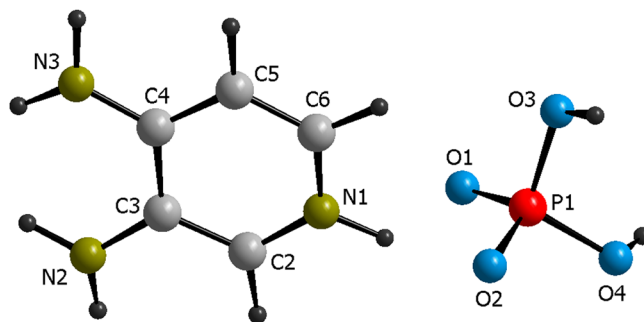
Figure 1. (Color online) Rietveld plot for 3,4-diaminopyridin-1-ium dihydrogen phosphate, $[C_5H_3(NH)(NH_2)_2]^+ (H_2PO_4)^-$. Calculated diffraction pattern as solid line, observed as dots, difference curve in the lower part, and positions of reflections as vertical bars.
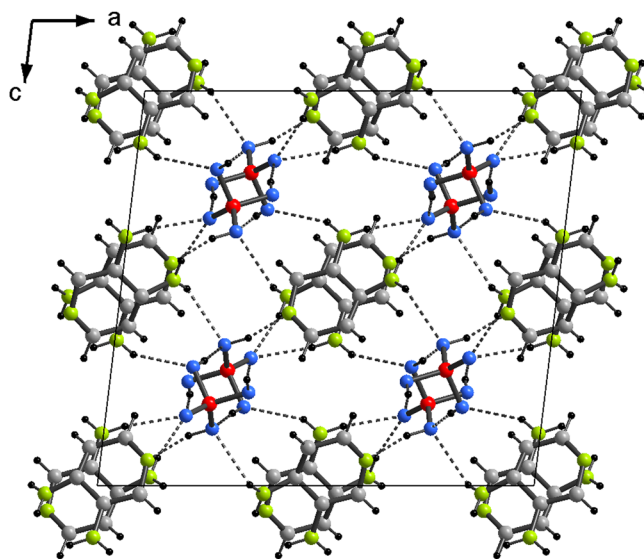
Figure 3. (Color online) Crystal packing of the 3,4-diaminopyridin-1-ium dihydrogen phosphate viewed along the b-axis. Dashed lines indicate hydrogen bonds.

TABLE II. Fractional atomic coordinates and isotropic displacement parameters ($Å^2$) for the 3,4-diaminopyridin-1-ium dihydrogen phosphate. The coordinates obtained by energy minimization in the solid state are listed in the bottom lines. For H atoms, the first line gives the coordinates as suggested by SHELXL in the cocrystal hypothesis.

	x	Y	z	U_{iso}
Nl	0.3922 (4)	0.2643 (13)	0.0636 (4)	0.073 (2)
	0.3883	0.2528	0.0624	
H1	0.3050	0.3089	0.1265	0.088
	0.3314	0.2805	0.0871	
N2	0.4956 (5)	0.3582 (11)	−0.1315 (4)	0.073 (2)
	0.4956	0.3703	−0.1342	
H2a	0.4541	0.4115	−0.1677	0.088
	0.4507	0.4476	−0.1677	
H2b	0.5466	0.3475	−0.1505	0.088
	0.5545	0.3780	−0.1529	
N3	0.6176 (4)	0.1991 (11)	−0.0209 (6)	0.073 (2)
	0.6250	0.2067	−0.0151	
H3a	0.6509	0.1114	0.0012	0.088
	0.6709	0.1602	0.0333	
H3b	0.6300	0.2599	−0.0700	0.088
	0.6437	0.2652	−0.0722	
C2	0.4003 (3)	0.3147 (16)	−0.0225 (4)	0.073 (2)
	0.4037	0.3209	−0.0192	
H2	0.3555	0.3512	−0.0634	0.088
	0.3525	0.3898	−0.059	
C3	0.4809 (3)	0.2921 (16)	−0.0458 (4)	0.073 (2)
	0.4816	0.3057	−0.0504	
C4	0.5485 (3)	0.2397 (12)	0.0199 (6)	0.073 (2)
	0.5467	0.2194	0.0082	
C5	0.5276 (4)	0.1483 (13)	0.0958 (6)	0.073 (2)
	0.5262	0.1473	0.0913	
H5	0.5659	0.0707	0.1289	0.088
	0.5737	0.0759	0.1355	
C6	0.4485 (3)	0.1757 (14)	0.1206 (5)	0.073 (2)
	0.4472	0.1657	0.1172	
H6	0.4340	0.1323	0.1774	0.088
	0.4282	0.1130	0.1805	
P	0.2659 (4)	0.5097 (9)	0.2072 (3)	0.088 (3)
	0.2682	0.5002	0.2101	
O1	0.3163 (5)	0.6515 (15)	0.1773 (7)	0.100 (3)
	0.3212	0.6475	0.1788	
O2	0.2526 (6)	0.3449 (14)	0.1440 (6)	0.100 (3)
	0.2492	0.3526	0.1404	
O3	0.3136 (5)	0.4414 (15)	0.3006 (6)	0.100 (3)
	0.3195	0.4270	0.3025	
H3	0.2896	0.3349	0.3166	0.15
	0.2938	0.3169	0.3259	
O4	0.1793 (5)	0.5718 (14)	0.2361 (6)	0.100 (3)
	0.1798	0.5643	0.2344	
H4	0.1869	0.6783	0.2685	0.15
	0.1796	0.6802	0.2695	

TABLE III. Selected bond distances (Å) and angles (°) for the 3,4-diamino-pyridin-1-ium dihydrogen phosphate obtained by the PLATON program (Spek, 2003). The values derived from energy minimization in the solid state are listed in the bottom lines.

Nl—C2	1.339 (9)	N1—C6	1.342 (10)
	1.346		1.355
N2—C3	1.399 (10)	N3—C4	1.359 (9)
	1.366		1.347
C2—C3	1.389 (8)	C3—C4	1.420 (8)
	1.388		1.436
C4—C5	1.390 (11)	C5—C6	1.379 (9)
	1.410		1.375
P—O1	1.461 (13)	P—O2	1.573 (12)
	1.526		1.536
P—O3	1.575 (10)	P—O4	1.577 (11)
	1.599		1.584
C2—N1—C6	126.7 (10)	N1—C2—C3	113.1 (8)
	121.95		121.61
N2—C3—C2	115.8 (8)	N2—C3—C4	120.8 (8)
	121.01		121.35
C2—C3—C4	122.0 (7)	N3—C4—C3	111.6 (8)
	117.64		121.16
N3—C4—C5	121.4 (11)	C3—C4—C5	116.5 (10)
	120.75		118.09
C4—C5—C6	116.7 (9)	N1—C6—C5	119.3 (9)
	120.94		119.67
O1—P—O2	118.2 (12)	O1—P—O3	106.3 (11)
	115.39		105.47
O1—P—O4	110.0 (10)	O2—P—O3	104.8 (9)
	112.45		109.84
O2—P—O4	110.0 (10)	O3—P—O4	102.9 (9)
	105.57		107.96

(Table III). As expected, the P-O bond distances fall into two groups, and the protonated P-O vertices show the expected lengthening of the P=O bonds (Blessing, 1988; Mahmoudkhani and Langer, 2002; Demir et al., 2003; Smrčok et al., 2009; Balamurugan et al., 2010; Kaman et al., 2011; Marouani et al., 2011). The structure of the 3,4-DAPP consists of dihydrogen phosphate tetrahedra linked by moderately strong (Jeffrey, 1997) O-H…O hydrogen bonds [Table IV and Figure 4(a)] involving all oxygen

TABLE IV. Hydrogen bond geometry of the 3,4-diaminopyridin-1-ium dihydrogen phosphate from the energy optimized coordinates.

D-H…A	D-H (Å)	H…A (Å)	D…A (Å)	D-H…A (°)
O3-H3…O2[a]	1.02	1.59	2.611	178
O4-H4…O1[b]	1.03	1.53	2.564	180
N1-H1…O2	1.04	1.71	2.739	169
N2-H2a…O3[c]	1.02	2.31	3.269	156
N2-H2b…O1[d]	1.02	2.08	3.093	170
N3-H3a…O2[e]	1.03	1.89	2.878	161
N3-H3b…O1[d]	1.02	1.85	2.869	175
C2-H2…O3[c]	1.09	2.48	3.402	142
C5-H5…O4[e]	1.09	2.36	3.450	177

[a] $1/2 − x, 1/2 − y, 1/2 − z$.
[b] $1/2 − x, −1/2 − y, 1/2 − z$.
[c] $x, −y, 1/2 + z$.
[d] $−x, −y, 1 − z$.
[a] $−1/2 + x, 1/2 − y, z$.

deviation from the least-squares plane fit to all nonhydrogen atoms being only 0.039 Å (due to N3). The optimized bond distances and bond angles are in good agreement with the values derived from the single crystal data (Rubin-Preminger and Englert, 2007), though it is N2 which is significantly displaced by 0.131 Å from the plane in the 3,4-DAP. The phosphate group in 3,4-DAPP is a slightly deformed tetrahedra with a minimum spread of the O-P-O bond angles

TABLE V. X-ray diffraction data of 3,4-diaminopyridin-1-ium dihydrogen phosphate (Cu Kα_1).

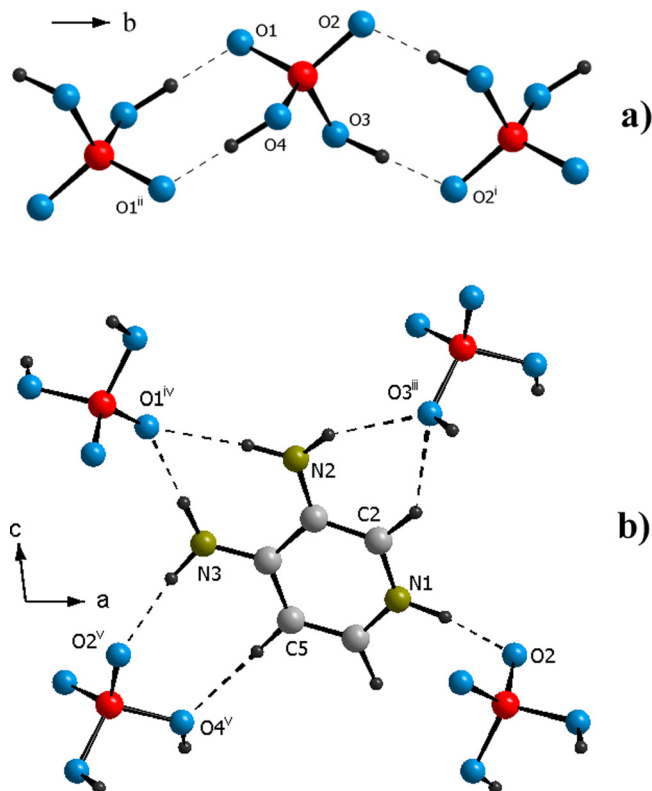| $2\theta_{obs}$ (°)	d_{obs} (Å)	I_{obs}	h	k	l	$2\theta_{cal}$ (°)	d_{cal} (Å)	I_{cal}	$\Delta 2\theta$ (°)
11.083	7.9767	7.1	2	0	0	11.080	7.9785	6.5	0.003
12.196	7.2511	2.8	0	0	2	12.186	7.2570	2.5	0.010
12.707	6.9610	2.8	1	1	0	12.714	6.9568	2.4	−0.007
15.474	5.7216	69.5	−2	0	2	15.479	5.7198	67.4	−0.005
17.169	5.1604	15.9	−1	1	2	17.177	5.1581	16.3	−0.008
17.457	5.0759	100.0	2	0	2	17.461	5.0748	100.0	−0.004
18.097	4.8978	6.0	1	1	2	18.104	4.8960	6.0	−0.007
20.239	4.3840	2.9	3	1	0	20.249	4.3819	2.9	−0.010
21.638	4.1036	4.5	0	1	3	21.652	4.1010	5.4	−0.014
22.261	3.9902	8.1	4	0	0	22.266	3.9893	8.4	−0.005
22.618	3.9280	9.8	−3	1	2	22.629	3.9262	13.2	−0.011
22.980	3.8669	3.6	0	2	0	22.991	3.8650	4.3	−0.011
24.108	3.6885	5.4	−4	0	2	24.118	3.6870	5.3	−0.010
24.289	3.6614	1.0	−1	2	1	24.287	3.6617	0.7	0.002
24.626	3.6121	9.6	1	2	1	24.626	3.6120	10.3	0.000
25.208	3.5300	2.6	−4	1	1	25.198	3.5314	2.2	0.010
25.583	3.4791	25.5	2	2	0	25.588	3.4784	30.2	−0.005
26.091	3.4125	39.7	0	2	2	26.100	3.4114	48.9	−0.009
26.735	3.3317	7.8	4	0	2	26.735	3.3317	8.9	0.000
27.091	3.2887	3.4	−1	1	4	27.095	3.2882	3.6	−0.004
27.833	3.2027	3.5	−2	2	2	27.836	3.2024	5.0	−0.003
28.296	3.1514	4.4	1	1	4	28.304	3.1505	7.4	−0.008
29.612	3.0142	8.1	−4	1	3	29.590	3.0165	1.8	0.022
			3	2	1	29.621	3.0133	9.3	−0.009
30.504	2.9281	10.8	1	2	3	30.512	2.9274	14.5	−0.008
31.239	2.8609	2.5	−4	0	4	31.250	2.8599	3.3	−0.011
31.412	2.8455	3.5	−5	1	2	31.421	2.8447	4.6	−0.009
32.199	2.7777	1.8	4	2	0	32.221	2.7759	2.8	−0.022
33.547	2.6691	2.5	3	1	4	33.555	2.6685	3.0	−0.008
35.496	2.5269	2.5	−6	1	1	35.503	2.5264	3.5	−0.007
36.048	2.4895	2.2	2	1	5	36.059	2.4887	3.0	−0.011
36.685	2.4477	1.5	2	2	4	36.680	2.4480	2.0	0.005
36.916	2.4329	1.1	6	1	1	36.929	2.4321	1.0	−0.013
39.483	2.2804	2.9	−5	2	3	39.490	2.2801	3.5	−0.007
			−6	0	4	39.510	2.2789	0.9	−0.027
39.744	2.2661	1.6	1	2	5	39.741	2.2662	2.3	0.003

Figure 4. (Color online) Details of hydrogen bonding in the structure of the 3,4-diaminopyridin-1-ium dihydrogen phosphate: (a) O-H…O bonds in the chains of dihydrogen phosphate moieties; (b) hydrogen bonds formed by the molecules of 3,4-diaminopyridin-1-ium cation. Symmetry codes are given at the bottom of Table IV.

atoms to the chains running along the *b*-axis. Antiparallelly, π–π stacked 3,4-DAP$^+$ cations form molecular columns in the spaces between the chains. The molecules are mutually slipped, but the perpendicular distances of the molecules are only ∼3.31 Å. Although the dominant interaction of the molecules with their surroundings is electrostatic, their bonding is further enhanced by the formation of N-H…O and C-H…O hydrogen bonds [Table IV and Figure 4(b)]. As a result, the architecture of hydrogen bonds comprise oxygen atoms, which are either acceptors or both donors and acceptors. Specifically, while the O1 and O2 atoms play only the role of acceptors of relatively strong O-H…O and N-H…O hydrogen bonds, the O3, except for playing a donor role in the phosphate chain, also receives a pair of a strong N-H and a weak C-H bonds. Finally, the donor O4 atom is also acceptor of a weak C-H…O bond. The N3…O1(O2) separations are comparable to the estimated mean values (∼2.85 Å) of the distribution of N…O contact distances extracted from CCSD database (Kumara Swamy *et al.*, 2001). On the contrary, the hydrogen bonds involving the

N2 atom are remarkably longer and hence weaker. The lengths of two C-H…O are comparable, but the bond angle in C5-H3…O4 is close to linear, and the bond is hence probably somewhat stronger.

IV. CONCLUSION

In the absence of a suitable single crystal, modern powder diffraction methodologies have the power sometimes to reveal crystal structures, including those of important pharmaceutical compounds. However, peak overlapping leads to unfavorable data/parameter ratios, and the crystal structures are often quite inaccurate without using restraints and constraints and even when using them. Moreover, not locating clearly H atoms may lead to difficulties to give the correct names to molecular compounds (in the cocrystallization hypothesis, the name would have been 3,4-diaminopyridine phosphoric acid). The presence of a single phase (no polymorph) in the sample studied is thus confirmed. Optimizing the atomic coordinates by quantum chemical calculations looks to be a complementary approach that will probably be soon generalized in such cases.

V. ACKNOWLEDGEMENT

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