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A Crystallographic Study of a Series of Nitrobenzoic Acid Co-crystals and Molecular salts

Scheepers, Matthew

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UNIVERSITY OF THE WITWATERSRAND
2019 -02- 25
FACULTY OF SCIENCE
REGISTRAR'S DEPT

Faculty of Science

Examiner 1

Division of Postgraduate Academic Management

EXAMINER'S REPORT ON A DISSERTATION SUBMITTED FOR THE AWARD OF MASTER OF SCIENCE

Name Of Candidate:	**Matthew Scheepers**
Person Number:	**706529**
Title of Dissertation:	**A Crystallographic Study of a Series of Nitrobenzoic Acid Co-crystals and Molecular salts**

Please read the information sheet before completing this form

	Examiner's Recommendation/s - Please answer all questions by ticking the appropriate box	YES	NO
1	Does the Dissertation reveal an adequate acquaintance with the methods of research? (Refer 2.1 of guide)	✓	
2	Is the literary presentation of the Dissertation satisfactory?	✓	
3	Does the Dissertation constitute a contribution to the advancement of knowledge in the subject chosen?	✓	
4	More than one category of b may be yes. Only **ONE** of c should be **YES** a) Do you recommend award of the degree of MSc for the Dissertation as it stands?		
	b) Do you recommend the award of the degree subject to: i) correction of minor errors **and/or**		
	ii) revision involving, for example, rewriting of certain sections **and/or**	✓	
	iii) extension, for example, additions of sections and/or provision of additional data?		
	c) If the answer to b) ii or b) iii is yes, i) Are you satisfied to leave the checking of the revised Dissertation to the Head of School?	✓	
	ii) Do you wish to re-examine the revised Dissertation?		
	d) Do you recommend outright rejection?		
5	Do you recommend the award of the degree with distinction? Please comment.		✓
6	The names of examiners are confidential, but successful candidates may be told the names of their examiners with their consent. Would you agree to your name being divulged in this case?		✓

EXAMINERS DETAILED REPORT

Please frame your report in the light of the requirements for the degree referred to in the Information Sheet. Please expand your recommendations under item 4 of this form. If you have suggested correction, revision and/or extension, please be specific about what the candidate should be required to do to make the Dissertation acceptable.

RECOMMENDATION /COMMENTS: SEVERAL IMPORTANT CHANGES NEED TO BE MADE WHICH INCLUDE WRITING A NEW SECTION ON PKA AND ADDING ONE OR TWO NEW CHAPTERS DISCUSSING AND COMPARING THE CRYSTAL STRUCTURES OF SELECTED AMINOPYRIDINES AND SELECTED DINITROBENZOIC ACIDS. DETAILS ARE GIVEN IN THE REPORT.

EXAMINER'S REPORT

15 February 2019

Candidate: Mr Matthew Scheepers (student number 706529)

Recommendation: Major Corrections and revisions are required.

A Crystallographic Study of a Series of Nitrobenzoic Acid Co-crystals and Molecular salts

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This MSc dissertation gives an account of the preparation of, crystallographic and thermal analysis of different crystalline forms of co-crystals or salts involving (i) four different substituted nitrobenzoic acids together with (ii) co-formers which include a number of substituted pyridines, urea, thiourea, and two different active pharmaceutical ingredients (APIs): Flufenamic Acid and Theophylline, dimethylaminobenzophenone, (trans)-Cinnamic Acid and Imidazole.

The dissertation is presented concisely in eight chapters (74 pages; or 61 pages excluding the appendix). Chapter 1, the introduction, gives a very brief literature review of the area of research (pharmaceutical drugs, crystal engineering and supramolecular chemistry, the hydrogen bond, crystal engineering and multi-component complexes (co-crystals and salts).

The hypotheses and aims of the research project are presented in point form at the end of this chapter. The structural diagrams of all of the nitrobenzoic acids and the co-formers used are given in a table at the end of this chapter, which comprise four nitrobenzoic acids and fifteen co-formers.

Chapter 2 briefly describes the characterization techniques and instrumentation and each of experimental methods employed. This covers only details of the crystallisation conditions, crystal data and X-ray structural analysis and Differential Scanning Calorimetry (DSC).

The subsequent three chapters are simply arranged according to which nitrobenzene was used in order to form the organic salt or co-crystal. Specifically each of these chapters deals with (i) The Co-crystals of 4-Nitrobenzoic Acid; Intro, CSD; (ii) The Co-crystals and Salts of 2-chloro-4-nitrobenzoic acid and 2-chloro-5-nitrobenzoic acids (iii) The Co-crystals of 3,5-Dinitrobenzoic Acid. Each chapter reports the crystal structures of each of the co-crystals or salts studied, following the same format throughout.

Appraisal

The technical details including crystal-structure refinements, ORTEP and packing diagrams, have been very well presented in the dissertation. Impressively, there are virtually no typographical errors. However, more has to be done in the introduction, aims and in particular in the results and discussion. A total of 21 crystal structures have been reported in this dissertation, four of which have been reported previously in literature. The 17 new crystal structures have been reported with very little or no comparison between them. Many co-crystals or salts are unrelated, which is a part of the problem.

Recommendations

My recommendations are in three parts, with reference to the introduction and specifically pKa, the aims and objectives, and to the need to add a chapter or two focusing on the comparison between specific co-crystals or salts. In the dissertation, pKa is only mentioned in one paragraph in section 1.3. This needs a separate section of at least 2-3 pages.

Recommendations for the Introduction

One of the key concepts in this research project is the pKa of ionisable organic molecules. This topic must be dealt with more extensively in the introduction.

(i) define pKa
(ii) explain how the pKa affects speciation (and, for example consider the Henderson-Hasselbalch equation describes the relationship between pH and pKa
(iii) give examples of where the so-called "pKa rule" has been successful or not successful in predicting whether a salt or co-crystal forms and
(iv) explain the effect of solvent. pKa is defined for an aqueous solution. None of the solvents used in this project are water.

There are numerous references that can be used for this discussion, the best are probably

a. Cruz-Cabeza AJ. Acid–base crystalline complexes and the p K a rule. CrystEngComm. 2012;14(20):6362-5. (Reference [7] in this dissertation) and
b. Lemmerer A, Govindraju S, Johnston M, Motloung X, Savig KL. Co-crystals and molecular salts of carboxylic acid/pyridine complexes: can calculated pK a's predict proton transfer? A case study of nine complexes. CrystEngComm. 2015;17(19):3591-5. This reference is important in discussing both pKa and salts or co-crystals of various pyridine molecules with chloronitrobenzoic acids. Surprisingly none of the supervisor's publications were cited in this dissertation.

Desiraju has also made significant contributions to this area of research. Of his numerous papers, one is a good guide on how to study co-crystals. Summarise some of his ideas in the introduction. (See Mukherjee A, Desiraju GR. Combinatorial exploration of the structural landscape of acid–pyridine cocrystals. Crystal Growth & Design. 2014 Feb 16; 14(3):1375-85. (SOLHOS, where NH_2 was replaced by NMe_2, and other related structures).

Recommendations for the Aims

The stated aims of this project are to synthesise co-crystals on a series of nitrobenzoic acids, and characterize these co-crystals by DSC and SC-XRD. This is simply a routine analysis. How were the nitrobenzoic acids and the co-formers selected? For example were they selected on the basis of pKas in order to test the pKa rule? There must be some sort of justification; otherwise, it is simply a random collection of co-formers with no specific hypothesis in mind. Some co-formers, such as urea and thiourea, do not seem to fall into any category (pages 11-15). Do you want to test if co-crystals or salts will form on the basis of pKas and/or potential hydrogen bonding? Expand and change the section 1.4, (Hypothesis and Aims) to consider these comments. There is no explicit hypothesis.

For example, for all of the nitrobenzoic acids selected (4-Nitrobenzoic acid; 2-Chloro-4-nitrobenzoic acid; 2-Chloro-5-nitrobenzoic acid; 3,5-Dinitrobenzoic acid), the pKas are similar, ranging from 2.04 (2c4n) to 3.42 (4nba). Only three of the pKas of the co-formers are below 3.5, so it is unsurprising that

most of the crystals formed were salts (Table 6 and Section 6 "Analysis of the pKa Rule" need to be revised.

Recommendations for the Results and Discussion

I would recommend the addition of at least one, possible two chapters. In this chapter, give a detailed comparison between selected co-crystals/salts that are chemically or structurally similar. Perhaps the most obvious structures to compare are the co-crystals/salts of aminopyridines with nitrobenzoic acids or chloronitrobenzoic acids.

There are several such comparisons in the literature that can be used as a guideline, one being the paper by Lemmerer et al (2015, CrystEngComm). There are many others, which can be found from the REFCODES in some of the tables in the dissertation or from additional CSD searches. I list some of them here:

- Sugiyama T, Meng JB, Matsuura T. Two-component molecular crystals composed of chloronitrobenzoic acids and 4-aminopyridine. Acta Crystallographica Section C: Crystal Structure Communications. 2002 Apr 15;58(4):o242-6; Note: These authors succeeded in making the FOUR co-crystals with chloronitrobenzoic acids and 4-aminopyridine. Why? What were their crystallization conditions and solvents?
- Some of the structures in Jin S, Zhu Q, Wei S, Wang D. Eight salts constructed from 4-phenylthiazol-2-amine and carboxylic acid derivatives through combination of strong hydrogen bonding and weak noncovalent interactions; Jin S, Zhu Q, Wei S, Wang D. Eight salts constructed from 4-phenylthiazol-2-amine and carboxylic acid derivatives through combination of strong hydrogen bonding and weak noncovalent interactions. Journal of Molecular Structure. 2013 Oct 8;1049:132-48;
- Gotoh K, Ishida H. Hydrogen-bonded structures of the isomeric compounds of quinoline with 2-chloro-5-nitrobenzoic acid, 3-chloro-2-nitrobenzoic acid, 4-chloro-2-nitrobenzoic acid and 5-chloro-2-nitrobenzoic acid. Acta Crystallographica Section C: Crystal Structure Communications. 2009 Oct 15;65(10):o534-8;
- Lemmerer A. Covalent assistance to supramolecular synthesis: modifying the drug functionality of the antituberculosis API isoniazid in situ during co-crystallization with GRAS and API compounds. CrystEngComm. 2012;14(7):2465-78;
- Tan T. Supramolecular helical architecture from the self-assemblies of 2-chloro-5-nitro-benzoic acid and organic bases. Journal of Molecular Structure. 2007 Sep 17;840(1-3):6-13.

EXAMINER'S REPORT

15 February 2019

Corrections to be made to the MSc dissertation

Candidate: Mr. Matthew Scheepers (706529) (School of Chemistry)

MSc dissertation:

"A Crystallographic Study of a Series of Nitrobenzoic Acid Co-crystals and Molecular salts"

General comments

In Tables 3.2, 4.2.1, 4.2.2, 5.2 give the full references, not just the REFCODES. There are a number of these references that should also be used in the comparison of co-crystals and salts of nitrobenzoic acids as mentioned above.

CHAP 3. The structure of 4nba(-) + 4-aminopyridinium has been reported previously. The candidate only compares the R-factor, stating that the one is this research is better. A more detailed justification must be given, not just the R-factor. For example, the hydrogen must be disordered over two sites in this study. It requires further discussion and comparison with reported structure. (Reference [18] in the dissertation; C.K. Quah, S.R. Jebasa, H. Fun, ActaCryst. E. 2008, 64, o1878–o1879. (CUZDAC). See also ORFCEV which has aminopyridinium + 4nba(-) +4nba. ORFCEV were 4-Aminopyridine and 4-nitrobenzoic acid were mixed in equimolar ratio in methanol, whereas CUZDAC Crystals of (I) used in the present work were obtained by slow evaporation from an equimolecular solution of NPNO and PNBA in absolute ethanol.

Presumably, the majority of benzoic acids + conformers selected did NOT form co-crystals or salts. Out of the 60 possible co-crystals, only 21 crystal structures are reported. Some that have been reported in literature were not obtained in this study (for example those with 4-amino-pyridine (see CSD).

Some discussion about possible reasons for this is essential, although it is often not possible to identify specific reasons. One publication that may help in this regard is Wahl H, Haynes DA, Le Roex T. Lack of co-crystal formation with cyclotriphosphazenes: a cautionary tale. South African Journal of Chemistry. 2016; 69:35-43.

Examiner 2

UNIVERSITY OF THE WITWATERSRAND
13 MAR 2019
FACULTY OF SCIENCE
REGISTRAR'S DEPT

Awaiting Hard copy from the examiner

Faculty of Science

Division of Postgraduate Academic Management

EXAMINER'S REPORT ON A DISSERTATION SUBMITTED FOR THE AWARD OF MASTER OF SCIENCE

Name Of Candidate: Matthew Scheepers

Person Number: 706529

Title of Dissertation: A Crystallographic Study of a Series of Nitrobenzoic Acid Co-crystals and Molecular salts

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		YES	NO
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	i) correction of minor errors **and/or**		✓
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	ii) Do you wish to re-examine the revised Dissertation?		✓
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RECOMMENDATION /COMMENTS:

Attached to email

15 March 2019

Examiners report

Dissertation: A Crystallographic Study of a Series of Nitrobenzoic Acid Co-crystals and Molecular Salts

Candidate: Matthew Scheepers

Summary

The dissertation by Matthew Scheepers describes the synthesis and characterization of 22 co-crystals and molecular salts of nitrobenzene and nitrobenzene derivatives (2-chloro-4-nitrobenzoic acid, 2-chloro-5-nitrobenzoic acid, 3, 5-dinitrobenzoic acid and 4-nitrobenzoic acid). Some of the co-crystals were analyzed in terms of the ΔpK_a and all were subjected to thermal analysis. Electronic crystal structure data was not included.

Chapter 1: The introduction presents a variety of topics related to understanding co-crystallization such as supramolecular chemistry and crystal engineering. However, the author appears to have glossed over these topics providing the reader with only very basic information. For example, the author chose to frame crystal engineering in the context of crystal structure prediction and crystal properties without relating both to the arrangement molecules in 3-dimensions or even relating crystal engineering to the definition of a crystal. More is needed. Moreover, the hypothesis, aims and objectives are not clearly delineated while within these sections the references have been used very sparingly. This requires urgent attention.

Chapter 2: The methods and materials section contains only the standard set of parameters and descriptors reported for these techniques. It does not convey any sense that the author understands these techniques. Please add descriptions of each of the techniques used during the study.

Chapters 3, 4 and 5: This is an enormous amount of work for an MSc dissertation! Even though this is a highly commendable achievement it does not make up for the fact that there is minimal analysis of the results. There are few comparisons between the data sets/co-crystals/salts. Categorizing the structures in terms of hydrogen bonding scheme should not be the only method

of analysis/interpretation, especially in the context of a crystallographic investigation. Why were the PXRD diffractograms not discussed in these chapters? Instead, the PXRDs have been included as part of the appendix. Please move these and discuss.

Chapters 6 and 7: In Chapter 6 the formation of salt or co-crystal is briefly assessed in terms of ΔpK_a. Why are there only 15 out 22 complexes listed in Table 6? Also, the paragraph on p56 ends with the statement, 'such as the case with the dnbaH-thp cocrystal,' – this is an incomplete statement and I am not sure what to make of this open ended proclamation. In Chapter 7, the DSC of dnba(-)-3apH shows two endothermic events. The author suggests that it is a dehydration event. Why was a TGA experiment not carried out to quantify the amount of included solvent? Surely this would help in the characterization of the material.

Finally, the number of salts/cocrystals isolated is undermined only by the literary presentation adopted by the author. There are many errors (typos) in the text and many ideas that are not well developed in the introduction. I have made these indications (typos) to the text of the dissertation and I leave their completion to the satisfaction of the Head of School.

Indeed, it is clear to see that nitrobenzoic acid and its derivatives are excellent co-formers. So, why not choose a co-former without a nitro group – would that not have made for an interesting comparison? Also, it is not clear from the text whether the author attempted the cocrystallization of the various nitrobenzoic acids on the same set of coformers. This could have added some interesting conclusions too.

Finally, I am satisfied that the author has an adequate acquaintance with the methods of research but I feel that the quality of the writeup should be higher. Therefore, I award this thesis only 55%.