

Table of contents

Scope of this thesis	1
I Crystallographic background	3
1 From experiment to structure	5
1.1 X-ray diffraction	6
1.2 The phase problem in crystallography	7
2 Experimental phasing	11
2.1 X-ray absorption and radiation damage	12
2.2 Isomorphous replacement	14
2.3 Anomalous dispersion	15
2.4 Substructure determination	19
2.5 Density modification	22
3 Heavy-atom derivatisation	25
3.1 Introduction	26
3.2 Soaking	26
3.3 Co-crystallisation	28
II Materials and methods	29
4 Synthesis of sticky triangles	31
4.1 Introduction	32
4.2 Iodinated compounds	32
4.3 Brominated compounds	32
4.4 Conclusion	37
5 Crystallisation and heavy-atom derivatisation	39
5.1 Crystallisation of small molecules	40
5.2 General remarks on protein crystallisation and heavy-atom derivatisation . .	40
5.3 Soaking	41
5.4 Co-crystallisation	43

6	Data collection, processing and refinement	45
6.1	Small-molecule crystallography	46
6.2	In-house data collection	46
6.3	Data collection at the synchrotron	46
6.4	Integration and scaling	47
6.5	Experimental phasing	47
6.6	Model building, refinement and validation	47
6.7	Radiation damage	48
III	Results and discussion	49
7	I3C - The magic triangle	53
7.1	Introduction	54
7.2	I3C crystal structure	54
7.3	Experimental phasing with I3C	56
7.4	Conclusion	60
8	B3C - The MAD triangle	63
8.1	Introduction	64
8.2	B3C crystal structure	65
8.3	MAD phasing with B3C	67
8.4	SAD phasing with B3C	72
8.5	Conclusion	73
9	More sticky triangles	75
9.1	Introduction	76
9.2	Crystal structures	77
9.3	Experimental phasing	80
9.4	Binding sites for B3M, B3O and B3C	82
9.5	Conclusion	84
10	B4C - The MAD tetragon	87
10.1	Introduction	88
10.2	B4C crystal structure	88
10.3	Experimental phasing	89
10.4	B4C binding sites	92
10.5	Conclusion	95
11	Exploiting the triangles for phasing	97
11.1	Searching for triangles: <i>TRIFIND</i>	98
11.2	Difficult structures with I3C	100
11.3	Tests with <i>SHELXD</i>	103
11.4	Conclusion	104

12 What makes the triangles sticky?	107
12.1 Interaction modes of the phasing tools	108
12.2 Triangles as additives in crystallisation screens	116
12.3 Conclusion	117
13 Summary and perspective	119
IV Appendix	121
A Novel protein structures solved with the magic triangle I3C	123
B Crystallographic parameters	129
C Crystallographic data for proteins	135
D Crystallographic data for small molecules	139
E Experimental data for small molecules	145
F Sticky triangles in the news	149
Bibliography	151
List of abbreviations	165
List of figures	169
List of tables	173
Scientific contributions	175
Acknowledgments	179
Curriculum Vitae	181