CHAPTER VI
CONCLUSIONS

Successful chiral separations of profens have been demonstrated on Chiralpak AD and Chiralcel OD. A systematic approach for optimization of the separation of racemic profens on both CSPs has been attained by varying the concentration of the alcoholic mobile phase modifier first, starting from the possible highest composition that would give a homogeneous eluent, while keeping the concentration (about 0.1%) of the strong acidic modifier, such as TFA, constant. A good choice of alcoholic modifier to start with is ethanol. Because of its polarity rapid optimization is possible due to short analysis time. Further enhancement of enantioseparation can be achieved by changing the nature of the alcoholic modifier. Once the optimized mobile phase condition of hexane/alcohol/0.1% acid modifier is known, the concentration of the acidic modifier could then be adjusted to improve the enantioselectivity of the chiral analyte. Final optimization could then be achieved by varying the column temperature last.

Enantioseparation of profens on Chiralpak AD was favored by either ethanol or 2-propanol as the alcoholic modifier, and TFA or HFBA as the acidic mobile phase modifier. Tert-butyl alcohol and HOAc as the alcoholic and acidic mobile phase modifiers, respectively, resulted to a decrease in enantioselectivity. From the temperature dependence studies, chiral separation on Chiralpak AD is said to be enthalpy controlled, hence lowering the temperature improved enantioselectivity.

On Chiralcel OD, on the other hand, chiral separations were more favored when *tert*-butyl alcohol was the alcoholic mobile phase modifier. Either TFA or HFBA could be used as the acidic modifier. In addition, lowering the temperature could either increase or decrease enantioselectivity depending on the analyte structure. Enantioseparation on Chiralcel OD is either enthalpy or entropy controlled.

The retention mechanisms for the separation of racemic profens on Chiralpak AD and Chiralcel OD are dependent primarily on the hydrogen bonding interaction between the acidic proton of the carboxyl moiety of the analyte and the carbonyl oxygen of the carbamate moiety of the CSP. This hydrogen bonding also affects enantioselectivity

which illustrates that the retention and chiral recognition mechanisms on both CSPs are complex and interrelated.

The chiral recognition mechanism on Chiralpak AD for racemic profens involves: (1) the formation of transient diastereomeric analyte-CSP complexes by reciprocal hydrogen bonding interactions between the carboxyl moiety and the carbamate moiety, respectively; (2) insertion into chiral cavities, as well as π-π and dipole-dipole interactions, for the stabilization of diastereomeric complexes; and (3) additional hydrogen bonding which is the driving force for chiral discrimination, which also contributes to the stabilization of diastereomeric complexes.

On Chiralcel OD, the two chiral recognition mechanism involve: (1) the formation of transient diastereomeric analyte-CSP complexes by two hydrogen bonding interactions between the carboxyl and carbamate moieties of analyte and CSP, respectively; (2) insertion to chiral cavities, and π-π and dipole-dipole interactions for the stabilization of diastereomeric complexes; and (3) chiral recognition by: (a) the difference of the steric fit of racemic analytes in a chiral cavity (entropy controlled) and (b) π-π or dipole-dipole interactions between analytes and CSP (enthalpy controlled). From the temperature dependence studies, it is apparent that there are two mechanisms operating on Chiralcel OD. Chromatographic and quantitative thermodynamic evidences were the favorable enantioseparations profens with “free” phenyl moieties were favorable at higher temperatures. Whereas the separations of those racemic analytes with fused rings at lower temperature.

The enantioseparating abilities of Chiralpak AD and Chiralcel OD appear to be dependent on their higher order structures. Variation of the mobile phase composition and the nature of the alcoholic and acidic mobile phase modifiers had significant effects on enantioselectivity on both CSP. Racemic profens showed different optimum enantioselectivities on the CSPs. In addition, there was a reversal in the order of the enantioselectivity of profens. This result also strongly suggests that the enantioseparating abilities of Chiralpak AD and Chiralcel OD were complementary from the viewpoint of racemic profens separated.

In summary, the work in this dissertation has demonstrated that chiral separations on derivatized polysaccharide CSPs, such as Chiralpak AD and Chiralcel OD are complex.

The chiral recognition depends on the higher order structure, thus, it is difficult to predict their chiral recognition only from the character of the tris(3,5-dimethylphenylcarbamate)-D-glucose monomer unit. For chiral separation optimization and mechanism studies, the chemistry of the analyte, CSP, and mobile phase should be taken into considerations. This research has contributed to the understanding of the separation of chiral compounds, specifically the profens of 2-methylarylpropionic acids on derivatized polysaccharides CSPs, as well as advanced some methodology with which the enantioseparation could be improved.

LITERATURE CITATIONS

1 C.J. Welch, in P.R. Brown and E. Grushka (Editors*), Advances in Chromatography*, Vol. 35, Marcel Dekker, Inc., New York, 1995, p.172.

2 S. Ahuja, in S. Ahuja (Editor), *Chiral Separation by Liquid Chromatography*, American Chemical Society, Washington, D.C., 1991, Ch. 1, p.1.

3 S. Lam and G. Malikin, *Chirality*, **4** (1992) 395.

4 I.W. Wainer (Editor*), Drug Stereochemistry Analytical Methods and Pharmacology*, Marcel Dekker, Inc., New York, New York, 1993.

5 ibid.

6 D.E. Drayer, *Clin. Pharmacol. Theor*., **40** (1986) 125.

7 G. Blaschke, H.P. Kraft, K. Fickentscher and F. Kohler, *Arneiz.-Forsch*., **29** (1979) 1640.

8 S.C. Stinson, *Chemical and Engineering News*, **70** (1995) 44.

9 B. Lin, X. Zhu, B. Koppenhoeffer and U. Epperlein, *LC·GC*,**15** (1997) 40.

10 P. van Eikeren, in S. Ahuja (Editor*) Chiral Separations Applications and Technology*, American Chemical Society, Washington, D.C., 1997, Ch. 2.

11 D.R. Taylor and K. Maher, *J. Chromatogr. Sci*., **30** (1992) 67.

12 Ahuja, op. cit., p. 43.

13 S. Allenmark, *Chromatographic Enantioseparation: Methods and Applications*, Ellis Horwood, Chichester, England, 1991, Ch. 3.

14 ibid.

15 A.M. Kristulovic (Editor), *Chiral Separations by HPLC: Applications to Pharmaceutical Compounds*, Ellis Horwood, Chichester, England, 1989.

16 Allenmark, op. cit.

17 ibid.

18 W. Boehme, G. Wagner and U. Oehme, *Anal. Chem*., **54** (1982) 709.

19 N. Purdie and K.A. Swallows, *Anal. Chem*., **61** (1989) 77A.

20 Allenmark, op. cit.

21 Taylor, op. cit.

22 R.A. Thompson, Z. Ge, N. Grinberg, D. Ellison and P. Tway, *Anal. Chem*., **67** (1995) 1580.

21 Y. Okamoto and Y. Kaida, *J. Chromatogr*. *A*, **666** (1994) 403.

22 Chiral Technologies, *Application Guide for Chiral Column Selection*, 2nd ed.

23 B. Koppenhoefer, A. Nothdurft, J. Pierrot-Sanders, P. Piras, C. Popescu, C. Roussel, M. Stiebler and U. Trettin, *Chirality*, **5** (1993) 213.

24 I.W. Wainer, *A Practical Guide to the Selection and Use of HPLC Chiral Stationary Phases*, J.T. Baker, Phillipsburg, N.J. 1988.

25 A. Berthod, S.C. Chang and D.W. Armstrong, *Anal. Chem*. **64** (1992) 395.

26 U. Norrinder and J. Hermansson, *Chirality*, **3** (1991) 422.

27 W.H. Pirkle and C.J. Welch, *J. Liq. Chromatogr*., **14** (1991) 2027.

28 W.H. Pirkle and T.C. Pochapski, *Chem. Rev*., **89** (1989) 347.

29 F. Jamali, R. Lovlin and G. Aberg, *Chirality*, **9** (1997) 29.

30 F. Jamali and D.R. Brocks, *Clin. Pharmacokin*., **19** (1990) 197.

31 F. Jamali, in I.W. Wainer (Editor), *Drug Stereochemistry: Analytical Methods and Pharmacology*; Marcel Dekker, Inc., New York, Ch. 14, p. 375.

32 ibid.

33 F. Jamali, *Eur. J. Drug Metab. Pharmacokinet*., **13** (1988) 1.

34. J. Caldwell, A.J. Hutt and S. Fournel-Gigleux, *Biochem. Pharmacol*., **37** (1988) 105.

35 F. Jamali, R. Methvar and F.M. Pasutto, *J. Pharm. Sci*., **78** (1989) 695.

36 R.T. Foster, F. Jamali, A.S. Russell and S.R. Alballa, *J. Pharm. Sci*., **77** (1988) 191.

37 Jamali, Lovlin and Aberg, op. cit.

38 C.S. Chen, W.R. Shieh and P.H. Lu, Harrin, Acta., **1078** (1991) 411.

39 Y. Tanaka, Y. Shimomura, T. Hirota, A. Nozaki, M. Ebata, W. Takasaki, E. Shigehara, R. Hayashi and J. Caldwell, *Chirality*, **4** (1992) 342.

40 A.V. Overbeke, W. Baeyens and C. Dewaele. *J. Chromatogr*., **18** (1995) 2427.

41 I.W.Wainer and T. Doyle, *J. Chromatogr*., **284** (1984) 117.

42 M. Yagi, A. Shibukawa and T. Nakagawa, *Chem. Pharm. Bull*., **38** (1990) 2513.

43 A. Shibukawa, A. Terakita, J.-Y. He and T. Nakagawa, *J. Pharm. Sci*., **81** (1992)

710.

44 J.B. Crowther, T.R. Covey, E.A. Dewey and J.D. Henion, *Anal. Chem*., **56** (1984) 2921.

45 D.A. Nicoll-Griffith, *J. Chromatogr*., **402** (1987) 179.

46 A. Scioufi, D. Colussi, F. Marfil and J.P. Dubois, *J. Chromatogr*., **414** (1987) 131.

47 W.H. Pirkle and J.E. McCune, *J. Chromatogr*., **471** (1989) 271.

48 D.A. Nicoll-Griffith, T. Inaba, B.K. Tang and W. Kalow, *J. Chromatogr*., **428** (1988) 103.

49 D. M. McDaniel and B.G. Snider, *J. Chromatogr*., **404** (1987) 123.

50 S.V. Kakodkar and M. Zief, *Chirality,* **2** (1990) 124.

51 W.H. Pirkle and P.G. Murray, *J.Liq. Chromatogr*., **13** (1990) 2123.

52 S.R. Perrin, *Chirality,* **3** (1991) 188.

53 M.H. Yang and J.-Y. Lin, *J. Chromatogr*., **631** (1993) 165.

54 M.H. Hyo, S.M. Cho, J.-J. Ryoo, M.S. Kim, D.A., *J. Liq. Chromatogr*., **17** (1994) 317.

55 H.-Y. Ahn, G.K. Shiu, W.F. Trafton, and T.D. Doyle, *J. Chromatogr*., **653** (1994) 163.

56 I.W. Wainer and M.C. Alembik, *J. Chromatogr*., **358** (1986) 85.

57 J. Hermansson and M. Eriksson, *J. Liq. Chromatogr*., **378** (1986) 409.

58 S. Menzel-Soglowek, G. Geisslinger and K. Brune, *J. Chromatogr*., **532** (1990) 295.

59 K.-J. Petterson and A. Olsson, *J. Chromatogr*., **563** (1991) 414.

60 G. Geisslinger, S. Menzel-Soglowek, O. Schuster and K. Brune, *J. Chromatogr*., **573** (1992) 163.

61 J.V. Andersen and S.H. Hansen, *J. Chromatogr*., **577** (1992) 362.

62 T. Miwa, T. Miyakawa and M. Kayano, *J. Chromatogr*., **408** (1987) 316.

63 J. Iredale, A.-F. Aubry and I.W. Wainer, *Chromatographia*, **31** (1991) 329-334.

64 Y. Oda, N. Asakawa, Y. Yoshida and T. Sado, *J. Pharm. Biomed. Anal*., **10** (1992) 81.

65 M.C. Banks, A. Fell and R.D. McDowall, *Anal. Proc*., **30** (1993) 98.

66 S. Allenmark and S. Anderson, *Chirality*, **1** (1989) 154.

67 A. Berthod, H.L. Jin, T.E. Beesley, J.D. Duncan and D.W. Armstrong, *J. Pharm. & Biomed. Anal*., **8** (1990) 123.

68 D.W. Armstrong, T.J. Ward, J.D. Armstrong and T.E. Beesley, ***Science***, **232** (1986) 1132.

69 T.A. Noctor, G. Felix and I.W. Wainer, *Chromatographia*, **31** (1991) 55.

70 T. Miwa, T. Miyakawa and Y. Miyake, *J. Chromatogr*., **457** (1988) 227.

71 J. Haginaka, T. Murashima and C. Seyama, *J. Chromatogr*., **677** (1994) 229.

72 Y. Okamoto, R. Aburatani, Y. Kaida, K. Hatada, N. Inotsume and M. Nakano, *Chirality*, **1** (1989) 239.

73 M.E.Y. Cabusas, Y.V. Kazakevich and H.M. Mcnair, Oral Presentation, PittCon 1996.

74 M.E.Y. Cabusas, Y.V. Kazakevich and H.M. Mcnair, Poster Presentation, EAS 1996.

75 T.D. Booth and I.W. Wainer, *J. Chromatogr*., **737** (1987) 157.

76 Y. Tang, *Chirality*, **8** (1996) 136.

77 R. J. Bopp and F. Geiser, Oral Presentation, PittCon 1997.

78 R. Lovlin, M. Vakily and F. Jamali, *J. Chromatogr. B*, **679** (1996) 196.

79 K. Ikeda, T. Hamasaki, H. Kohno, T. Ogawa and T. Matsumoto, J. Sakai, *Chem. Lett*., (1989) 1089.

80 Overbeke, op. cit.

81 McDaniel, op. cit.

82 Okamoto, Aburatani, Kaida, Hatada, Inotsume and Nakano, op. cit.

83 Booth, op. cit.

84 P. Pescher, M. Caude, R. Rosset and A. Tambute, *J. Chromatogr*., **371** (1986) 159.

85 H. Lamparczyk, P.K. Zarzycki and J. Nowakowska, *J. Chromatogr. A*, **668** (1994) 413.

86 D.T. Witte, J.-P. Franke, F.J. Bruggeman, D. Dijkstra and R.A. de Zeeuw, *Chirality* (1992) 389.

87 Okamoto, Aburatani, Kaida, Hatada, Inotsume and Nakano, op. cit.

88 Booth. op. cit.

89 Wainer and Alembik, op. cit.

90 Ahuja, op. cit.

91 G.M. Loudon, *Organic Chemistry*, Addison-Wesley Publishing Co., Massachusetts, 1984, pp. 231-234.

92 L. Pasteur, *Am. Chim., Phys*. **24** (1848) 442.

93 Loudon, op. cit.

94 M. Zief and L.J. Crane (Editors), *Chromatographic Chiral Separations*, Marcel Dekker, Inc., New York, (1988) Ch. 1.

95 ibid.

96 J.H. van't Hoff, *Arch. Neerl. Sci Exactes. Natur*., **9** (1874) 445.

97 J.A. Le Bel, *Bull. Soc. Chim. Paris*, **22** (1874) 337.

98 Loudon, op.cit.

99 Kristulovic, op. cit.

100 G.M. Henderson and H.G. Rule, *J. Chem. Soc*. (1939) 1568.

101 M. Kotake, T. Sakan, N. Nakamura and S. Senon, *J. Am. Chem. Soc. ,* **73** (1951) 2973.

102 C.E. Dalgliesh, *J. Chem. Soc*., **47** (1952) 3940.

103 Pirkle and Pochapski, op. cit.

104 L.H. Klemm and D. Reed, *J. Chromatogr*., **3** (1960) 364.

105 E. Gil-Av, B. Feibush and R. Charles-Siegler, *Tetrahedron Lett*. (1996) 1009.

106 Zief, op. cit., Ch. 1.

107 Ahuja, op. cit., Ch. 1.

108 Taylor, op. cit.

109 ibid.

110 Wainer and Doyle, op. cit.

111 Zief, op. cit., Ch. 4.

112 ibid.

113 R.W. Souter, *Chromatographic Separation of Stereoisomers*, CRC Press, Boca Raton, 1985.

114 Zief, op. cit.

115 Allenmark, op. cit.

116 Ahuja, op. cit.

117 Taylor, op. cit.

118 ibid.

119 Wainer, op. cit.

120 Pirkle and Pochapski, op. cit.

121 N. Oi, *Bunseki Kagaku*, **33** (1984) E 401.

122 Y. Dobashi and S. Hara, *Tetrahedron Lett*., **26** (1985) 4217.

123 J.N. Akanya, S.M. Hitchen and D.R. Taylor, *Chromatographia*, **16** (1982) 224.

124 R. Dappen, V.R. Meyer and H. Arm, *J. Chromatogr*., **295** (1984) 367.

125 W. Lindner and I. Hirschbock, *J. Pharm. and Biomed. Anal*., **2** (1984) 183.

126 Ahuja, op. cit., Ch. 6.

127 W. Pirkle, *J. Org. Chem*., **57** (1992) 3854.

128 D. Bees and R. Skerret, *Carbohydr. Res*., **7** (1968) 334.

129 D. Voet and J. Voet, *Biochemistry*, John Wiley and Sons, New York, 1990, pp. 254-257.

130 G. Gubitz, W. Jellenz, and D. Schonleber, *J. High Resol. Chromatogr. Commun*., **3** (1980) 31.

131 S. Yuasa, M. Itoh and S. Shimada, *J. Chromatogr. Sci*., **22** (1984) 288.

132 A. Chimiak and J. Polonski, *J. Chromatogr*., **115** (1975) 635.

133 B. Frank and G. Blaschke, *Liebigs Ann. Chem*., **695** (1966) 144.

134 W. Mayer and F. Merger, *Liebigs Ann. Chem*., **644** (1961) 651.

135 G. Hesse and R. Hagel, *Chromatographia*, **6** (1973) 277.

136 A. Ichida, T. Shibata, Y. Okamoto, Y. Yuki, H. Namikashi and Y. Toga, *Chromatographia*, **19** (1984) 280.

137 Y. Okamoto, R. Aburatani, S. Miwa and K. Hatada, *J. Liq. Chromatogr*., **10** (1987) 1613.

138 Y. Okamoto, M. Kawashima, R. Aburatani, K. Hatada, T. Nishiyama and M. Masuda, *Chem. Lett*. (1986) 1237.

139 Y. Okamoto and Y. Kaida, *J. Chromatogr. A*, **666** (1994) 403.

140 Y. Okamoto, R. Aburatani, Y. Kaida, K. Hatada, N. Inotsume and M. Nakano,

Chirality, **1** (1989) 239.

141 Wainer and Alembik, op. cit.

142 I.W. Wainer, R. Stiffin and T. Shibata, *J. Chromatogr*., **411** (1987) 139.

143 Witte, op. cit.

144 Wainer and Alembik, op. cit.

145 T. Shibata, I. Okamoto and K. Ishii, *J. Liq. Chromatogr*., **9** (1986) 313.

146 Wainer, op. cit., Ch. 6.

147 Booth, op. cit.

148 Okamoto and Kaida, op. cit.

149 ibid.

150 ibid.

151 Ahuja, op. cit, Ch. 4.

152 ibid.

153 D.W. Armstrong and A..M. Stalcup, *Anal. Chem*., **62** (1990) 1610.

154 A. Berthold, D.W. Armstrong and W. Li, *Anal. Chem*., **64** (1992) 873.

155 J.M. Timko, R. Hegelson, M. Newcomb, G. Gokel and D.J. Cram, *J. Am. Chem. Soc*., **96** (1974) 7097.

156 G. Dotsevi, Y. Sogah and D.J. Cram, *J. Am. Chem. Soc*., **97** (1971) 1259.

157 T. Shinbo, T. Yamaguchi, K. Nishimura and M. Suguira, *J. Chromatogr*., **405** (1987) 145.

158 V.A. Davankov and A.V. Somechkin, *J. Chromatogr*., **141** (1977) 313.

159 S.V. Rogozhin and V.A. Davankov, Ger. Pat., 1 932 190 (1970); Russ. Pat. Appl., (1968); C.A., 72 (1970) 90875C.

160 S.V. Rogozhin and V.A. Davankov, *Chem. Commun*., (1971) 490.

161 G. Gubitz, W. Jellenz and W. Santi, *J. Chromatogr*., **203** (1981) 377.

162 B. Feibush, M.J. Cohen and B.L. Karger, *J. Chromatogr*., **282** (1983) 3.

163 L.R. Gelber, B.L. Karger, J.L. Neumeyer and B. Feibush, *J. Am. Chem. Soc*., **106** (1984) 7729.

164 K.K. Stewart and R.F. Doherty, *Proc. Natl. Acad. Sci. USA*, **70** (1973) 2850.

165 S. Allenmark and B. Bomgren, *J. Chromatogr*., **365** (1982) 297.

166 J. Hermansson, *J. Chromatogr*., **269**, (1983) 71.

167 T. Miwa, M. Ichikawa, M. Tsuno, T. Hattori, T. Miyakawa, M. Kayano and Y. Miyake, *Chem. Pharm. Bull*., **35** (1987) 682.
168 T.A.G. Noctor, G. Felix and I.W. Wainer, *Chromatographia*, **31** (1991) 55.
169 T. Miwa, T. Miyakawa and Y. Miyake, *J. Chromatogr*., **1988**, 457 (1988) 227.
170 P. Erlandsson, I. Marle, L. Hansson, R. Isaksson, C. Petterson and G. Petterson, *J. Am. Chem. Soc*., **112** (1990) 4573.
171 Ahuja, op. cit., Ch. 6.
172 ibid.
173 W. Melander, D. E. Campbell and C. Horvath, *J. Chromatogr*., **158** (1978) 215.
174 ibid.
175 W.S. Hancock, D.R. Knighton, J.R. Napier and D.R. Harding, *J. Chromatogr*., **367** (1986)1.
176 Melander, 1978, op. cit.
177 L.A. Cole and J.G. Dorsey, *Anal. Chem*., **64** (1992) 1317.
178 K.G. Feitsma, J. Bosman, B.F.H. Drenth and R.A. De Zeeuw, *J. Chromatogr*., **333** (1985) 59.
179 D.J. Mazzo, C.J. Lindemann and G.S. Brenner, *Anal. Chem*., **58** (1986) 636.
180 P. Pescher, M. Caude, R. Rosset and A. Tambute, *J. Chromatogr*., **371** (1986) 159.
181 L.E. Weaner and D.C. Hoerr, *J. Chromatogr*., **437** (1988) 109.
182 ibid.
183 R.K. Gilpin, S.E. Ehtesham and R.B. Gregory, *Anal. Chem*., **63** (1991) 2825.
184 Berthold, op. cit.
185 Witte, op. cit.
186 K. Cabrera and D. Lubda, *J. Chromatogr. A*, **666** (1994) 433.
187 R.J. Smith, D.R. Taylor and S.M. Wilkins, *J. Chromatogr. A*, **697** (1995) 591.
188 T.D. Booth and I. W. Wainer, *J. Chromatogr. A*, **741** (1996) 205.
189 W. Pirkle and C. Welch, *J. Liq. Chromatogr*., **14** (1991) 2027.
190 Zief, op. cit. Ch. 12.
191 Loudon, op. cit.
192 M. Zief, L.J. Crane and J. Horvath, *J. Liq. Chromatogr*., **7** (1984) 709.

193 Pescher, op. cit.

194 P. Macaudiere, A. Tambute, M. Caude, R.H. Rosset, M.A. Alembik and I.W. Wainer, *J. Chromatogr*., **371** (1986) 177.

195 H. Koller, K.-H. Rimbock and A. Mannschreck, *J. Chromatogr*., **282** (1983) 89.

196 I.W. Wainer, M.C. Alembik and E. Smith, *J.Chromatogr*., **388** (1987) 66.

197 Y. Okamoto, R. Aburatani, Y. Kaida and K. Hatada, *Chem. Lett*. (1988)1125.

198 Y. Tang, *Chiralit*, **8** (1996) 136.

199 Okamoto, Aburatani, Kaida, Hatada, Inotsume and Nakano, op. cit.

200 Booth and Wainer, op. cit.

201 Tang, op. cit.

202 W.H. Pirkle, D.W. House and J.M. Finn, *J. Chromatogr*., **192** (1980) 143.

203. G. Hesse and R. Hagel, *Chromatographia*, **9** (1976) 62.

204 G. Blaschke, *Angew. Chem*., **92** (1980) 14.

205 E. Francotte, R.M. Wolf, D. Lohmann and R. Mueller, *J. Chromatog*r., **347** (1985) 25.

206 D.W. Armstrong, *J. Liq. Chromatogr*., **7** (Supplement 2) (1984) 353.

207 Wainer and Alembik, op. cit.

208 I.W. Wainer, M.C. Alembik and E. Smith, *J. Chromatogr*., **388** (1987) 65.

209 Wainer and Stiffin, op. cit.

210 Witte, op. cit.

211 Melander, Campbell and Horvath, op. cit.

212 Kaliszan, *Quantitative Structure-Chromatographic Retention Rrelationship*, Wiley-Interscience, New York, 1987)

213 R. Kaliszan, K. Osmialowski and R.A. Hartwick, *J. Chromatogr*. **352** (1986) 141.

214 P. Jandera, *J. Chromatogr*. **314**(1984) 13.

215 K. Jino, K. Kawasaki, *Chromatographia*, **18** (1984) 90.

216 R. Kaliszan, T.A.G. Noctor and I.W.Wainer, *Chromatographia*, **33** (1992) 546.

217 Booth and Wainer, **737**, op. cit.

218 Booth and Wainer, **741**, op. cit.

219 ibid.

220 Melander, op. cit.

221 K.B. Lipkowitz, *J. Chromatogr. A*, **694** (1995) 15.

222 P. Camilleri, J.A. Murphy, M.R. Saunder and C.J. Thorpe, *J. Computer-Aided Mol. Design*, **5** (1991) 277.

223 ibid.

224 Allenmark, op. cit.

225 Pirkle and Popchapski, op. cit.

226 Taylor, op. cit.

227 Pirkle and Popchapski, op. cit.

228 ibid.

229 Okamoto, Aburatani, Kaida, Hatada, Inotsume and Nakano, op. cit.

230 Taylor, op. cit.

231 Wainer and Alembik, op. cit.

232 Wainer and Stiffin, op. cit.

233 P. W. Atkins, *Physical Chemistry*, W.H. Freeman & Co., New York, (1994) p.763.

234 ibid.

235 ibid.

236 J.E. Huheey, *Inorganic Chemistry Principles of Structure and Reactivity*, Harper and Row, Publishers, New York (1978) p. 242.

237 ibid

238 V. Schurig, J. Chromatogr. A 666 (1994) 111.

239 Allenmark, op. cit.

240 Pirkle and Pochapski, op. cit.

241 Schurig, op. cit.

242 A. Bethjod, W. Li and D.W. Armstrong, *Anal. Chem.*, **64** (1992) 973.

243 Schurig, op. cit.

244 B. Koppenhoeffer and E. Bayer, *Chromatographia*, **19** (1984) 123.

245 V. Schurig and F. Betschinger, *Chem. Rev.*, **92** (1992) 873.

246 K. Watabe,R. Charles and E. Gil-Av, *Angew. Chem., Int. Ed. Engl.*, **28** (1989)192.

247 B. Koppenhoeffer and B. Lin, *J. Chromatogr.*, **481** (1989) 17.

248 V. Schurig, J. Ossig and R. Link, *Angew. Chem., Int. Ed. Engl.*, **28** (1989)194.

249 Schurig, op. cit.

250 ibid.

251 Melander, op. cit.

252 ibid..

253 ibid.

254 ibid.

256 Pirkle and Welch, op. cit.

257 K. Oguni, H. Oda and A. Ichida, *J. Chromatogr. A,* **694** (1995) 91.

258 Okamoto and Kaida, op. cit.

259 Vogt and Zugenmaier, op. cit.

260 ibid.

261 Okamoto and Kaida, p. 413.

263 Taylor, op. cit.

264 Okamoto, Aburatani *et al*., op. cit.

265 Wainer and Alembik, op. cit.

266 Witte, op. cit.

267 ibid.

268 Booth, op. cit.

269 ibid.

270 O'Brien, L. Crocker, R. Thompson, K. Thompson, P.H. Toma, D.A. Conlon, B. Feibush, C. Moeder, G. Bicker and N.Grinberg, *Anal. Chem. Soc*., **69** (1997)1999.

271 ibid.

272 ibid.

273 A. Ichida, T. Shibata, I. Okamoto, Y. Yuki, H. Namikoshi and Y. Toga, *Chromatographia*, **19** (1984) 280.

274 Y. Okamoto and M. Kawashima and K. Am, *Chem. Lett*. (1984) 739.

275 Zief, op. cit., Ch. 9.

276 ibid.

277 Okamoto, Kawashima and Am, op. cit.

278 Y. Okamoto and M. Kawashima and K. Am, *J. Am. Chem. Soc*., **106** (1984) 5357.

279 A. Gupta, E. Marchal and W. Burchard, *Macromolecules,* **8** (1975) 843.

280 P. Maissa, M. Seurin and P. Sixou, *Polym. Bull*., **15** (1986) 257.

281 R. Issalkson, P. Erlandsson, L. Hansson, A. Holmberg and S. Berner, ***J. Chromatogr***., **498** (1990) 257.

282 K. Kamide and M. Saito, in H.Clark , K. Kamide, S. Ross-Murphy and M. Saito Eds.) *Advances in Polymer Science*, Springer, Berlin, 1987, vol. 83.

283 Booth, op. cit.

284 Loudon, op. cit.

285 Vogt, op. cit.

286 ibid.

287 L. Rohrscneider, *Anal. Chem*., **45** (1973) 1241.

288 L.R. Snyder, *J. Chromatogr*., **92** (1974) 223.

289 Booth, op. cit.

VITA

Maria Elena Y. Cabusas was born in May 31, 1960, during her parents' third wedding anniversary, in Iligan City, Philippines. She started her elementary grade at the age of six, and finished it with honors in April of 1972. For her higher studies, she thrived on fellowships. She entered Mindanao State University - Iligan Institute of Technology for her high school, which was geared for engineering and engineering technology courses, and graduated in April of 1976. She was in the second experimental batch of students taking advanced courses in mathematics, physics, and chemistry. After being granted a full scholarship by the Mindanao State University, Philippines, she initially entered the University as a chemical engineering major. In her senior year, she changed her field to chemistry after learning, partly, that the engineering job competition for women is tough. She finished her B.S. in Chemistry in April of 1981, within the required five years. In June of 1981 she joined the Chemistry Department of the Mindanao State University - Iligan Institute of Technology and was trained to teach college chemistry courses. She taught both lectures and laboratory for general chemistry courses, and organic chemistry and biochemistry for biology majors. In June of 1985 she was granted a fellowship to pursue Master's in Chemistry at the University of the Philippines. She was temporarily swept away by the big change of environment and was then testing the challenge of one job to another. From November of 1986 to April 1987, she was a part- time lecturer of De La Salle University, Philippines. She taught both lectures and laboratory in general chemistry and biochemistry courses. Next, she accepted a research assistantship under the direction of Dr. Elma LLaguno at the Natural Sciences Research Institute of the University of the Philippines. From July 1989 to May 1991, she was deeply involved in the isolation and physical characterization of humic substances from water, soil, sediment, and peat samples. She gained valuable laboratory skills specially on the different sampling and extraction techniques and physical characterization methods, as well as working knowledge of water and soil chemistry. Moreover, she gained skills in managing the laboratory and supervising the research of undergraduate students. From June 1991 to December 1993, she joined the Chemistry Faculty of the University of the Philippines. She taught both lectures and laboratories for

general chemisty and biochemistry courses, as well as gave laboratory instructions for analytical, physical, and organic chemistry courses. From January 1994 until March 1998 she studied at Virginia Tech under the direction of Prof. Harold McNair, helping teach several American Chemical Society GC, GS-MS, and HPLC short courses, and acting as a teaching assistant for the general chemistry courses. Apart from chiral HPLC research, she did works on the influence of pH and ionic strength on the separation of polar and ionizable compounds by reversed phase HPLC, method developments for the analysis of imidazoles and plasticizers in water samples by reversed phase HPLC, and synthesis of organic compounds such as C_6I_6. In addition, from May 15 until August 15 of 1997, she worked as a Senior Co-op Technician at SmithKline Beecham, Philadelphia. She did impurity profile analysis and method development for the industrial hygiene monitoring of a newly synthesized asthma drug by reversed phase HPLC and LC-MS. Upon graduation, Maria Elena Cabusas accepted a Research Chemist position at the Experimental Station of Dupont Agricultural Products in Wilmington, Delaware.