Principal Properties for Synthetic Screening: Amines

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Carlson, R., Prochazka, M. P. and Lundstedt, T., 1988. Principal Properties for Synthetic Screening: Amines. – Acta Chem. Scand., Ser. B 42: 157–165.

Principal properties of amines were determined by principal components (PC) analysis of data for a set of 126 amines. Each amine was characterized by seven property descriptors. A two-component PC model was significant according to cross validation, and accounted for 85 % of the variance of the descriptor data.

Primary and secondary amines were described by the same PC model as for the tertiary amines, which indicated that hydrogen bonding is not significantly involved in determining the physical properties of amines.

Factors that determine the chemical behaviour of amines are discussed. Principles for selecting test objects using the principal properties are briefly discussed.

Amines are an important class of compounds in organic synthesis. Numerous examples of electrophilic functionalization on the nitrogen can be given. Primary and secondary amines will thus give neutral species in which a proton is displaced. A rough estimate based on the pharmaceutical literature indicates that over 95 % of all commercially available pharmaceuticals are amine derivatives. Tertiary amines are often used as base catalysts and/or proton scavengers.

To explore new synthetic procedures, either for functionalizing amines or using amines as auxiliary reagents, it is desirable that test systems span a wide range of variation. It is also desirable that all important properties of the system are considered in this context.

In as series of papers we have described new principles for the selection of test objects in synthetic explorations. These methods are based on principal components (PC) analysis of property descriptors for series of potential test candidates. The significant components thus obtained are orthogonal measures of systematic variations and are called *principal properties*. Principal properties have hitherto been reported for organic solvents,[1] Lewis acids,[2] aldehydes,[3] ketones[3] and amino acids.[4] We have also discussed how principal properties can be used to explore the entire reaction space.[5]

A study of amine variation in the Willgerodt-Kindler reaction was based on principal properties of a small set of 29 primary and secondary amines.[6] However, to be of general and practical interest, selection of test objects must be made from a much larger collection of potential candidates. In this paper, which concludes our series of papers on principal properties for synthetic screening, we report a study of 126 commercially available primary, secondary and tertiary amines.

Data

The amines were characterized by seven property descriptors. Data are given in Table 1. The descriptors were compiled from different sources.[7] IR data were also considered initially, but these descriptors were deleted in the final analysis since they were not consistent over the whole data set; e.g. one compilation of literature data on amines[7a] contained data for the strongest IR absorption band which, however, referred to different chromophores. IR data were also missing for a number of amines.

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Table 1. Property descriptors and PC scores of amines.

Id.[a]	Amines	Descriptors[b]							PC scores	
		1	2	3	4	5	6	7	t_1	t_2
74	Allylamine	57.09	−88	1.4205	0.76	53.00	75.03	–	−2.65	−0.74
75	*N*-Allylcyclohexylamine	139.24	–	1.4664	0.96	–	144.74	–	1.48	−0.30
76	2-Amino-3,3-dimethylbutane	101.19	−20	1.4130	0.76	102.50	134.03	–	−1.01	0.81
77	2-Aminoheptane	115.22	–	1.4175	0.77	143.00	150.42	–	−0.60	1.08
73	2-Amino-2-methylbutane	87.17	–	1.3996	0.75	77.00	116.85	–	−2.03	0.51
23	2-Amino-2,3,3-trimethylbutane	129.25	–	1.4240	0.81	140.00	160.56	–	−0.14	1.08
78	Benzylamine	107.16	10	1.5424	0.98	184.50	109.24	9.33	1.54	−1.23
79	2-Benzylpyridine	169.23	9	1.5785	1.05	276.00	160.56	5.13	4.32	−1.30
80	3-Benzylpyridine	169.23	–	1.5815	1.04	287.50	162.41	–	4.39	−1.21
81	4-Benzylpyridine	169.23	–	1.5818	1.06	287.00	159.50	–	4.45	−1.36
82	Butylamine	73.14	−49	1.4010	0.74	78.00	98.84	10.65	−2.08	0.13
83	*sec*-Butylamine	73.14	−72	1.3928	0.72	63.00	101.02	10.63	−2.46	0.18
84	*tert*-Butylamine	73.14	−67	1.3790	0.70	46.00	105.09	10.69	−2.73	0.42
85	*N*-Butylbenzylamine	163.27	–	1.5006	0.91	–	179.22	–	2.43	0.45
86	*N*-(*tert*-Butyl)benzylamine	163.27	–	1.4968	0.88	–	185.32	10.19	1.99	1.07
71	Cyclobutylamine	71.12	–	1.4316	0.83	82.00	85.38	3.96	−0.91	−2.08
87	Cycloheptylamine	113.20	–	1.4724	–	–	–	–	0.41	−0.43
88	Cyclohexylmethylamine	113.20	–	1.4630	0.87	147.00	130.11	11.04	−0.07	0.19
89	Cyclohexylamine	99.18	−17	1.4580	0.87	134.00	114.39	10.66	−0.22	−0.13
90	*N*-Cyclohexyl-1,3-propanediamine	156.27	−16	1.4820	0.92	–	170.41	–	1.95	0.37
69	Cyclopentylamine	85.15	–	1.4482	0.86	107.00	98.66	10.65	−1.10	−0.52
70	Cyclopropylamine	57.09	–	1.4206	0.82	49.50	69.30	9.10	−2.31	−1.29
68	Decylamine	157.29	13	1.4360	0.79	217.00	199.87	10.64	1.30	2.09
91	Diallylamine	97.16	−88	1.4405	0.79	111.50	123.46	–	−1.21	0.06
67	Dibutylamine	129.25	−62	1.4170	0.77	159.00	168.51	11.25	−0.38	1.52
125	Di-*sec*-Butylamine	129.24	–	1.4110	0.75	135.00	171.63	–	−0.48	1.66
92	2,6-Di-*tert*-butyl-4-methylpyridine	205.35	34.5	1.4767	–	233.00	–	–	3.15	2.42
93	2,6-Di-*tert*-butylpyridine	191.32	–	1.4739	0.85	–	224.55	5.02	3.49	1.08
66	Dicyclohexylamine	181.32	−2	1.4842	0.91	256.00	199.25	–	2.84	1.12
94	Diethylamine	73.14	−50	1.3861	0.71	55.00	103.45	11.16	−2.49	0.47
65	*N,N*-Diethylcyclohexylamine	155.29	–	1.45622	0.85	195.00	182.69	–	1.36	1.16
64	*N,N*-Diethylmethylamine	87.17	–	1.3887	0.72	64.00	121.07	9.75	−2.09	0.40
95	Dihexylamine	185.36	–	1.4320	0.80	193.50	233.16	–	1.55	2.76
126	Diisoamylamine	157.29	–	1.4230	0.77	186.00	204.01	–	0.74	2.26
124	Diisopropylamine	101.19	−61	1.3920	0.72	84.00	141.13	10.96	−1.71	1.09

contd

Table 1. (contd)

Id.[a]	Amines	Descriptors[b]							PC scores	
		1	2	3	4	5	6	7	t_1	t_2
119	Dimethylamine	45.09	−93	1.3700	0.68	7.40	66.27	10.73	−3.89	−0.30
63	*N,N*-Dimethylbenzylamine	135.21	−75	1.5011	0.90	184.00	150.23	9.03	0.95	−0.17
96	1,3-Dimethylbutylamine	101.19	–	1.4085	0.72	109.00	141.13	–	−1.46	1.12
97	3,3-Dimethylbutylamine	101.19	–	1.4135	0.75	115.00	134.56	–	−1.23	0.79
98	*N,N*-Dimethylcyclohexylamine	127.23	–	1.4535	0.85	158.50	149.86	–	0.44	0.38
99	*N,N*-Dimethylethylamine	73.14	−140	1.3720	0.68	37.00	108.36	–	−3.67	0.79
62	1,5-Dimethylhexylamine	129.25	–	1.4209	0.77	155.00	168.51	–	−0.16	1.46
61	*N,N*-Dimethyloctylamine	157.29	−57	1.4243	0.76	195.00	205.62	–	0.52	2.26
100	1,4-Dimethylpiperazine	114.19	–	1.4463	0.84	131.00	135.30	–	−0.16	0.10
101	2,5-Dimethylpiperazine	114.19	–	–	–	164.50	–	–	0.82	−0.82
102	2,6-Dimethylpiperidine	113.20	–	1.4394	0.84	128.00	134.76	11.07	−0.49	0.47
103	3,5-Dimethylpiperidine	113.20	–	1.4454	0.85	144.00	132.71	–	−0.04	0.03
104	1,2-Dimethylpropylamine	87.17	−50	1.4055	0.76	85.50	115.15	–	−1.70	0.40
105	Dipentylamine	157.29	–	1.4272	0.78	202.50	202.45	–	0.94	2.18
60	Diphenylamine	169.23	53	–	–	302.00	–	0.79	6.52	−3.96
59	2,6-Diphenylpyridine	231.28	75	–	–	–	–	–	8.35	−1.64
106	Dipropylamine	101.19	–	1.4035	0.74	107.50	137.11	11.20	−1.44	0.98
58	Dodecylamine	185.36	29	–	–	248.00	–	10.67	4.99	−2.09
50	1-Ethynylcyclohexylamine	123.19	–	1.4817	0.91	–	134.94	–	1.00	−0.50
108	*N*-Ethylbutylamine	101.19	–	1.4050	0.74	108.00	136.74	–	−1.42	0.96
109	2-Ethylbutylamine	101.19	21.5	1.4209	0.78	125.00	130.39	–	−0.34	0.65
110	*N*-Ethylcyclohexylamine	127.23	–	1.4525	0.84	165.00	150.75	–	0.47	0.44
57	5-Ethyl-2-methylpyridine	121.18	–	1.4974	0.92	178.00	131.86	–	1.19	−0.75
56	4-Ethylmorpholine	115.18	−63	1.4415	0.90	139.00	127.27	–	−0.07	−0.33
51	1-Ethylpiperidine	113.20	–	1.4440	0.83	131.00	137.28	10.45	−0.37	0.40
52	2-Ethylpiperidine	113.20	–	1.4510	0.85	143.00	132.24	–	−0.01	−0.02
53	2-Ethylpyridine	107.16	–	1.4964	0.94	149.00	114.37	5.89	0.94	−1.62
54	3-Ethylpyridine	107.16	–	1.5015	0.95	166.00	112.34	5.70	1.19	−1.74
55	4-Ethylpyridine	107.16	–	1.5009	0.94	168.00	113.76	6.03	1.12	−1.60
107	Ethylamine	45.09	−81	–	0.69	19.50	65.44	10.70	−3.58	−0.39
49	Furfurylamine	97.12	−70	1.4900	1.10	145.50	88.37	–	0.81	−2.68
123	Heptylamine	115.22	–	1.4243	0.78	155.00	148.67	10.66	−0.41	0.97
111	1-Hexadecylamine	241.46	41	–	–	330.00	–	10.61	4.54	3.91
48	Hexylamine	101.19	−23	1.4180	0.77	131.50	132.10	10.64	−0.75	0.73
47	Isoamylamine	87.17	–	1.4089	0.75	96.00	116.07	10.60	−1.72	0.35
122	Isobutylamine	73.14	−85	1.3970	0.74	68.00	99.51	10.42	−2.44	0.03

contd

Table 1. (contd)

Id.[a]	Amines	Descriptors[b]							PC scores	
		1	2	3	4	5	6	7	t_1	t_2
112	Isopropylamine	59.11	−101	1.3756	0.69	33.50	85.17	10.71	−3.39	−0.01
46	*N*-Isopropylbenzylamine	149.24	–	1.5025	0.89	200.00	167.31	9.69	1.69	0.49
43	2-Methylbenzylamine	121.18	–	1.5435	0.98	199.00	124.03	9.19	1.66	−1.00
44	3-Methylbenzylamine	121.18	–	1.5360	0.97	203.50	125.45	9.45	1.58	−0.83
45	4-Methylbenzylamine	121.18	12.5	1.5340	0.95	195.00	127.29	9.54	1.73	−0.65
39	*N*-Methylbutylamine	87.17	–	1.3995	0.74	91.00	118.44	10.69	−1.88	0.50
40	1-Methylbutylamine	87.17	–	1.4029	0.74	91.00	118.44	10.65	−1.85	0.47
41	2-Methylbutylamine	87.17	–	1.4116	0.74	95.50	118.12	–	−1.77	0.48
42	*S*-(−)-2-Methylbutylamine	87.17	–	1.4126	0.74	–	118.12	–	−1.83	0.46
113	*N*-Methylcyclodecylamine	169.31	–	1.4832	0.98	–	172.41	–	2.66	0.18
35	*N*-Methylcyclohexylamine	113.20	–	1.4560	0.87	–	130.41	10.72	−0.15	0.16
36	2-Methylcyclohexylamine	113.20	–	1.4565	0.86	150.00	132.24	–	0.13	−0.10
37	3-Methylcyclohexylamine	113.20	–	1.4525	0.86	–	132.39	–	0.05	−0.06
38	4-Methylcyclohexylamine	113.20	–	1.4531	0.86	154.00	132.39	–	0.13	−0.05
34	4-Methylmorpholine	101.15	−66	1.4349	0.92	115.50	109.95	7.38	−0.26	−1.07
33	*N*-Methylphenethylamine	135.21	–	1.5162	0.93	203.00	145.39	9.35	1.65	−0.21
114	1-Methylpiperazine	100.17	–	1.4655	0.90	138.00	110.93	–	0.04	−0.92
29	1-Methylpiperidine	99.18	–	1.4378	0.82	106.50	121.54	10.38	−0.95	0.08
30	2-Methylpiperidine	99.18	–	1.4459	0.84	118.58	117.51	10.95	−0.80	0.02
31	3-Methylpiperidine	99.18	–	1.4470	0.85	125.50	117.37	11.07	−0.75	0.05
32	4-Methylpiperidine	99.18	–	1.4458	0.84	124.00	118.35	10.78	−0.75	0.03
28	*N*-Methylpropargylamine	69.11	–	1.4332	0.82	83.00	84.38	–	−1.73	−0.89
27	6-Methylquinoline	143.19	–	1.6135	1.06	259.00	134.70	5.15	3.93	−2.15
115	Morpholine	87.12	−6	1.4541	1.00	129.00	87.21	8.33	0.20	−1.54
26	Neopentylamine	87.17	–	1.4030	0.75	–	117.00	9.85	−1.72	0.25
25	Nonylamine	143.27	–	1.4548	0.78	201.00	183.21	10.64	0.87	1.55
24	Octadecylamine	269.52	51	–	–	–	–	10.60	5.16	4.50
22	Octylamine	129.25	−2	1.4290	0.78	170.00	165.28	10.65	0.27	1.37
72	Pentylamine	87.17	−50	1.4110	0.75	104.00	115.92	10.63	−1.51	0.39
21	Phenethylamine	121.18	–	1.5335	0.96	198.50	125.58	9.88	1.46	−0.73
20	*N*-Phenylbenzylamine	183.25	36.5	–	1.06	306.50	172.71	–	5.00	−1.01
19	4-Phenylmorpholine	163.22	52.5	–	–	–	–	–	7.76	−5.46
15	3-Phenyl-1-propylamine	135.21	–	1.5260	0.95	221.00	142.18	–	2.25	−0.87
16	2-Phenylpyridine	155.19	–	1.6242	1.09	269.00	142.90	4.77	4.44	−2.14
17	3-Phenylpyridine	155.19	–	1.6155	1.08	–	143.44	–	4.49	−2.21
18	4-Phenylpyridine	155.19	–	–	–	274.50	–	5.35	4.03	−1.40

contd

Table 1. (contd)

Id.[a]	Amines	Descriptors[b]							PC scores	
		1	2	3	4	5	6	7	t_1	t_2
12	Picoline	93.13	−70	1.5000	0.94	128.50	98.75	5.96	0.42	−2.08
13	3-Picoline	93.13	−19	1.5054	0.96	144.50	97.31	5.70	1.04	−2.09
14	4-Picoline	93.13	2	1.5050	0.96	145.00	97.31	5.99	1.16	−1.98
121	Piperazine	86.14	106	1.4460	–	146.00	–	9.83	1.05	0.60
116	Piperidine	85.15	−13	1.4525	0.86	106.00	98.90	11.20	−0.76	−0.31
11	Propargylamine	55.08	–	1.4480	0.80	83.00	68.59	8.15	−1.80	−1.54
10	Propylamine	59.11	−83	1.3889	0.72	48.00	82.21	10.69	−2.98	−0.16
9	Pyridine	79.10	−42	1.5090	0.98	115.00	80.88	5.25	0.57	−2.73
120	Pyrrolidine	71.12	–	1.4431	0.85	87.50	83.47	11.27	−1.73	−0.68
8	1-Tetradecylamine	213.41	41	–	–	–	–	10.62	3.58	3.28
117	Tetramethylpyrazine	136.20	85	–	–	190.00	–	2.80	4.53	−3.39
6	Tridecylamine	199.38	31	–	–	265.00	–	11.00	2.96	3.21
7	Triethylamine	101.19	−7	1.4000	0.73	88.80	139.38	10.85	−1.23	1.09
118	Trimethylamine	59.11	−117	–	0.64	–	92.94	9.80	−3.56	0.07
5	Trioctylamine	353.68	–	1.4485	0.81	366.00	437.18	–	6.75	7.43
2	Tripropargylamine	131.18	–	1.4838	0.93	–	141.51	–	1.33	−0.41
3	Tripropylamine	143.27	−94	1.4165	0.75	157.00	190.27	10.66	−0.42	1.75
4	Tris(dimethylamino)methane	145.25	–	1.4360	–	–	–	–	0.55	1.52
1	Undecylamine	171.33	17	1.4388	0.80	240.00	215.24	10.63	1.93	2.41

[a]Identification number used in the score plots. [b]Descriptors: **1**, molar mass (10^{-3} kg mol^{-1}); **2**, melting point (°C); **3**, refractive index; **4**, density (10^3 kg m^{-3}); **5**, boiling point (°C); **6**, molar volume (10^{-6} m^3 mol^{-1}); **7**, pK_a. Descriptors **1–5** were taken from Ref. 7a, **6** was calculated, **7** was compiled from various standard handbooks (Refs. 7b–d).

Methods

The principal properties were determined by fitting PC models to the data in Table 1. The SIMCA program package was used.[8] The number of significant components was determined by cross validation.[9] Prior to calculation of the PC models, each descriptor variable was scaled to unit variance (autoscaling). This was done to avoid distorting the variance through the use of

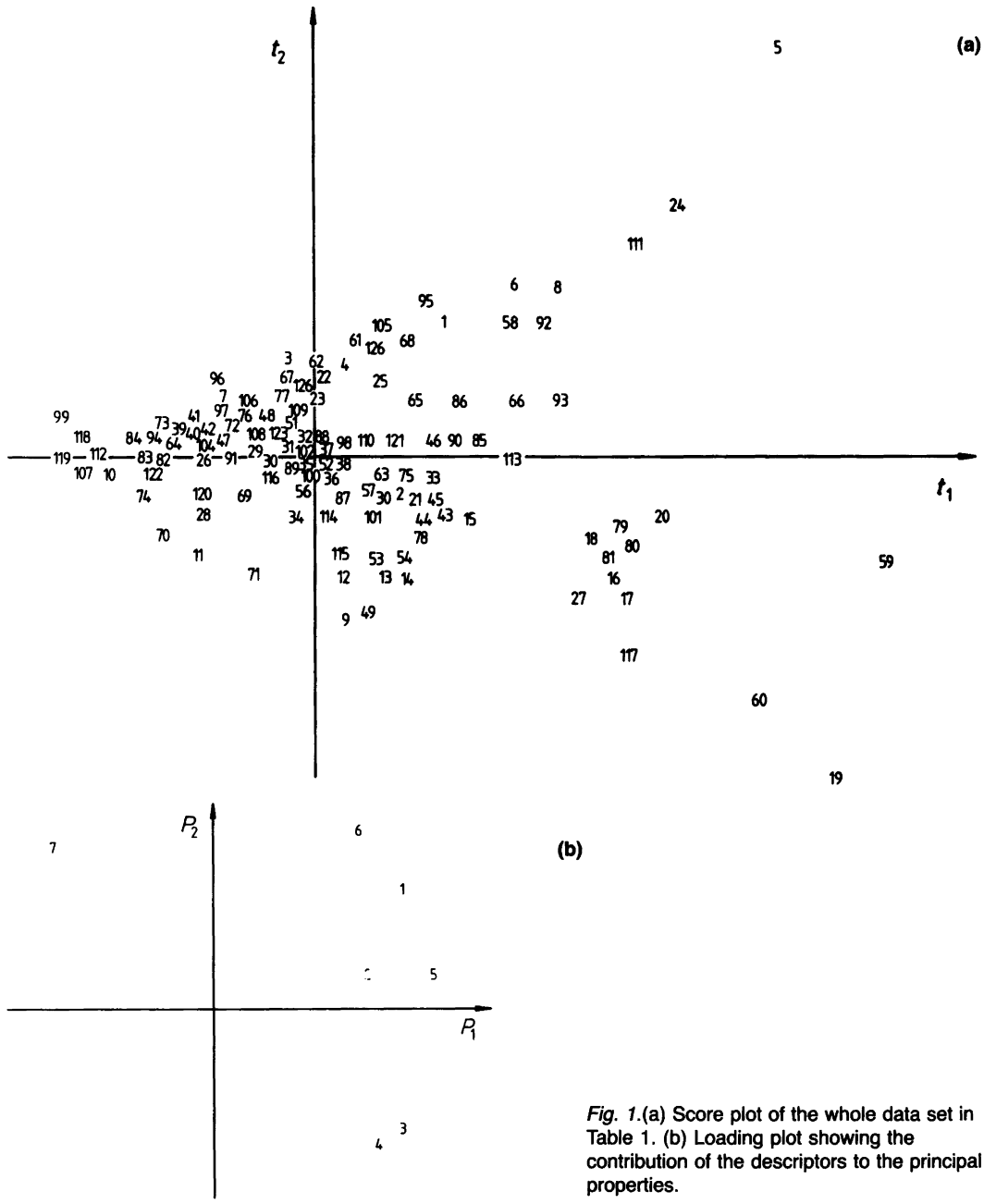

Fig. 1.(a) Score plot of the whole data set in Table 1. (b) Loading plot showing the contribution of the descriptors to the principal properties.

different units of measurement. Detailed accounts of PC analysis have been given elsewhere.[8,10]

Results

The data in Table 1 were analyzed as follows: To check the homogeneity of the data, a PC model was calculated from the whole data set. A two-component model was significant according to cross validation and accounted for 88 % of the total variance. For some amines, however, several data were missing; to prevent this introducing bias into the model, a calibration set of 95 amines were selected allowing a maximum of two missing data for each amine. A two-component model described 85 % of the variance. The principal properties were then determined by projecting the whole data set down to this model. The PC projections are shown in Fig. 1, and the PC scores (t values) are listed in Table 1. Two amines, viz. tetramethylpyrazine (No. 117) and piperazine (No. 121) were projected outside the 95 % confidence limits of the model.

Primary and secondary amines can form intermolecular hydrogen bonds which may influence their physical properties. To analyze whether this would require disjoint PC models for tertiary amines and for amines which can give rise to hydrogen bonding, PC models were fitted to training sets of either type of amine. In these training sets, a maximum of two missing data for each amine were allowed. The PC projection for the tertiary amines is shown in Fig. 2. However, projection of the whole data set in Table 1 onto either model afforded almost identical results. This shows that separate models for the two types of amines are not necessary.

Discussion

Descriptors. Missing data are always a problem when data are compiled for large sets of chemical compounds. This restricts the number of property descriptors, since only easily measured properties are commonly available.

The chemical behaviour of amines depends on at least four factors, viz. basicity, nucleophilicity, solvation and steric environment of the amine nitrogen.

Basicity. The only basicity descriptor generally available for a sufficiently large number of the amines in Table 1 is pK_a (measured in water). We conclude that this is sufficient for screening purposes since a projection almost identical to that given in Ref. 6 was obtained when the primary and secondary amines included in this previous study were projected onto the model calculated for the amines in Table 1. The basicity descriptors used to characterize the 29 primary and secondary amines in the previous study were, in addition to pK_a, proton affinity and gas-phase basicity.

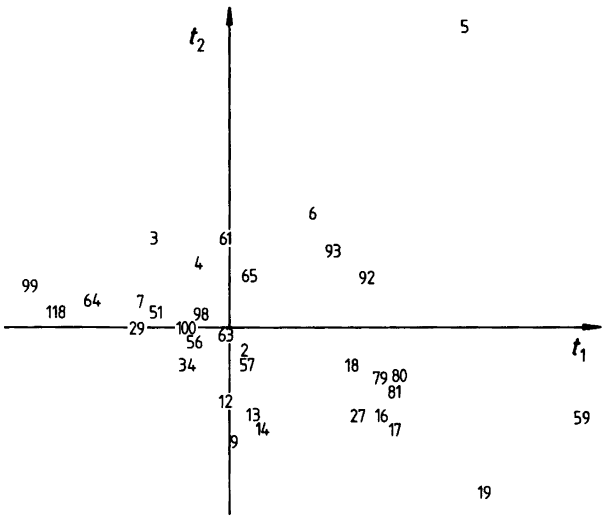

Fig. 2. Score plot for tertiary amines.

Nucleophilicity. It is difficult to obtain good descriptors for this property. Kinetic data for nucleophilic displacement reactions are available for only a few amines. Since nucleophilicity is, in part, dependent on the properties of the lone-pair electrons on the nitrogen, indirect measures related to this property must be used, for instance pK_b or some other basicity descriptor or refractive index, which is related to polarizability. These descriptors were used in the present study. There are other suitable data e.g. ionization potentials and frontier orbital energies, but these were unfortunately not available for a sufficiently large number of amines.

Solvation. The substrate and reagent may be differently solvated when the solvent is changed, which may alter the reactivity pattern. Principal properties can be used to design screening experiments in which both solvent and reagent are simultaneously varied.[5]

The unexpected result that tertiary amines afford the same PC model as primary and secondary amines shows that hydrogen bonding does not significantly influence physical properties such as melting point, boiling point and density. These properties must therefore depend on weak dispersion forces. Such forces are responsible for solvation in aprotic non-polar organic solvents commonly used in synthetic reactions. It has previously been shown that in absence of strong interactions, several properties in the liquid state can be adequately described by PC models.[11]

In strongly associated protic solvents, hydrogen bonding will be involved in solvation. This property is not covered by the descriptors used in the present study. In a situation in which both the amine and the solvent are to be jointly considered, such interaction will be accounted for by the principal properties of the solvent.

Steric environment of the amine nitrogen. This factor is not treated in the present analysis. It is suggested that steric factors should be considered separately as an additional criterion for selection based on the principal properties. A discussion of a similar problem, viz. selection of aldehydes and ketones on the basis of their principal properties, is given in Ref. 3.

Selection of test compounds. PC analysis reveals the systematic variation in all the descriptors. The score plot portrays this variation. Hence, such projections can be used to achieve selection of test objects in which *all* properties are considered *simultaneously*. Thorough discussions of the principles of such selections have been given in previous papers.[1–6] Here, only a brief summary is presented:

(A) Select test objects that are projected on the periphery of the score plot. This will give a selection which spans a large range in all properties considered.

(B) Select test objects that are uniformly spread over the score plot. This will give a selection in which a uniform spread in all properties is achieved.

Conclusions

The principal properties of amines are described by two principal components. The PC model accounted for 85% of the variation in a set of seven property descriptors. The property descriptors are related to factors which govern the chemical reactivity. Hence, an experimental design based on the principal properties will allow for selection of test compounds so that a sufficient variation in all important properties is achieved. This may lead to an increased efficiency in experimentation by allowing test objects to be easily selected so that a maximum of information can be obtained in the individual experiments.

Calculations

The calculations were carried out on a IBM PC-XT or IBM-compatible microcomputers. The SIMCA program package (SIMCA 3-B version) was used for modelling. The program is available from *Sepanova AB,* Östrandsvägen 14, S-112 43 Enskede, Sweden or from Principal Data Components, Shepard Blvd., Columbia, Missouri 65201, USA.

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