4812 *J. Phys. Chem. A* **2004,** *108,* 4812−4818

A Quantitative Structure−Property Relationship Study of Lithium Cation Basicities

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Received: November 25, 2003; In Final Form: February 25, 2004

A quantitative structure−property relationship (QSPR) study of the gas-phase lithium cation basicity of a diverse set of 205 compounds provided a general six-parameter QSPR model ($R^2 = 0.801$; $R^2_{cv} = 0.785$; $F = 133.11$; $s^2 = 8.78$) using the CODESSA PRO program. Theoretical molecular descriptors, such as the minimum net atomic charge, highest occupied molecular orbital energy, total point-charge component of the molecular dipole, etc., logically explain the reaction equilibrium and electrostatic interaction between a lithium cation and a base.

Introduction

Alkali metal ions were the first metal cations to be studied in the gas phase for their coordination properties. This can be understood by considering their relatively easy production under vacuum. In contrast with transition metal ions, their reactivity toward ligands is quite simple: in general, they form adducts, or clusters, that can be considered as ions “solvated” by one or several ligands. Moreover, the possibility of measuring accurate alkali metal cation affinities with high accuracy by means of (i) equilibrium constant determination by high-pressure mass spectrometry (HPMS),[1−5] (ii) ion cyclotron resonance (ICR),[6−10] (iii) unimolecular dissociation (the Cooks’ kinetic method),[11,12] (iv) energy-resolved collision-induced dissociation (CID),[13−15] and (v) photodissociation and radiative association kinetics[16−18] has stimulated a growing interest in the study of these interactions.[19−21] Such measurements generate a collection of data which help the understanding of fundamental interactions implied in analytical mass spectrometry, organic synthesis, catalysis, lithium battery electrochemistry,[22] and cation transport through ion channels.[23]

A book edited by Sapse and Schleyer[24] presents various aspects of the chemistry of lithium, the most individual alkali metal.

Gas-phase lithium cation basicity (LCB) is defined in eq 1 as the Gibbs free energy of eq 2 associated with the thermodynamic equilibrium of eq 3.

$$\mathrm{LCB} = -\Delta G_{\mathrm{Li}^+} \qquad (1)$$

$$\Delta G_{\mathrm{Li}^+} = -RT \ln K_1 \qquad (2)$$

$$\mathrm{B} + \mathrm{Li}^+ \overset{K_1}{\rightleftharpoons} [\mathrm{B}{-}\mathrm{Li}^+] \qquad (3)$$

In a similar manner, the gas-phase lithium cation affinity (LCA) is defined in eq 4 as the negative value of the enthalpy change of eq 3.

$$\mathrm{LCA} = -\Delta H_{\mathrm{Li}^+} \qquad (4)$$

When considered as Lewis acids, H^+ and Li^+ present a significant contrast in the nature of the bond formed with a ligand. A proton adds to a base, forming a polar covalent bond with a very extensive charge transfer (the positive charge on the hydrogen atom is usually 0.4 electronic unit or less, whereas the base molecule carries the rest of the positive charge). The large degree of charge transfer results from the fact that H^+ is a bare nucleus, with an unfilled 1s orbital of very low energy. In contrast, bonds formed by Li^+ (with its filled 1s shell) and other alkali metal cations are largely ionic, and the alkali metal cation retains 0.8−0.9 unit of the positive charge in such complexes.[25−32]

The first consistent, and relatively extensive, gas-phase scale of lithium cation basicities was published by Taft et al.[10] This scale is comprised of 110 typical bases covering the range of 23.2−46.9 kcal/mol (1 kcal/mol = 4.184 kJ/mol) of absolute LCB values and has been widely used for converting relative basicities to absolute ones and for obtaining the effective temperature of CID−FT−ICR experiments.[11,12]

The scale of gas-phase lithium cation basicities of simple monofunctional compounds was further extended to sulfuryl and phosphoryl derivatives.[33−35] However, Rodgers and Armentrout revealed flaws in the anchoring process:[14,15] (i) The relative LCBs determined in Taft’s laboratory corresponded to experiments carried out at 373 K, but erroneously anchored (reference compound, H_2CO) to the value evaluated by Woodin and Beauchamp[6,7] at 298 K. (ii) The Woodin and Beauchamp LCBs were obtained using entropies calculated by statistical mechanics procedures, which involved various simplifying assumptions. (iii) Woodin and Beauchamp based their LCB scale on a $Li^+{-}H_2O$ bonding energy value, which was based on a $Li^+{-}H_2O$ binding energy reported by Džidi and Kebarle,[1] that had been extrapolated from measurements made for larger $Li^+{-}(H_2O)_n$ clusters and not measured directly. Recently, the $Li^+{-}H_2O$ bond energy was measured by Rodgers and Armentrout[13] who concluded that the $Li^+{-}H_2O$ binding energy estimated by Džidi and Kebarle[1] was too high.

Numerous theoretical techniques[25−32,36−43] at different levels (ab initio and density functional theory, DFT) have been used to study the structure and thermodynamic properties (including lithium cation affinity) of the interaction between the Li^+ cation and different neutral and anionic bases. Most of these studies comprise a fairly small number of similar bases, and provide limited relationships between experimental and theoretically calculated LCA values.[32,38]

However, a major finding is that inclusion of electron correlation effects and the use of sufficiently large and flexible

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10.1021/jp037594n CCC: $27.50

TABLE 1: Experimental and Predicted LCB and Descriptors' Values

no.	compound	LCB(exp)	LCB(pred)	$q_{\min}$	Ns	HOMO-1	FPSA-1	u_c	HASA-2
1	1-(4-methylphenyl)-ethanone	38.15	38.84	−0.30	0	−9.92	0.63	2.89	6.42
2	1,1,1,3,3,3-hexafluoro-2-methoxypropane	26.23	26.49	−0.24	0	−13.43	0.26	3.58	0
3	1,1,1-trifluoro-2,4-pentanedione	35.33	33.43	−0.28	0	−11.95	0.33	2.50	12.56
4	1,1,1-trifluoroacetone	27.05	28.04	−0.27	0	−13.86	0.31	3.08	6.69
5	1,2,3-triazole	32.11	35.77	−0.21	0	−11.34	0.44	2.56	15.00
6	1,2,4-triazole	32.78	35.00	−0.20	0	−11.21	0.45	1.92	14.67
7	1,2-dimethoxyethane	44.91	32.85	−0.28	0	−10.71	0.82	0	0
8	1,2-dimethylimidazole	41.85	37.48	−0.17	0	−10.17	0.68	2.81	7.47
9	1,2-oxathiolane 2-oxide	39.11	38.15	−0.77	0.08	−11.09	0.74	4.78	0
10	1,3,4,5-tetramethylpyrazole	39.05	39.04	−0.18	0	−9.16	0.80	1.88	6.24
11	1,3,5-trimethylpyrazole	38.38	39.37	−0.23	0	−9.28	0.75	1.96	6.78
12	1,4-dimethylpyrazole	37.05	37.77	−0.18	0	−9.67	0.72	1.98	7.15
13	1,4-dioxane	30.35	31.01	−0.27	0	−11.42	0.79	0	0
14	1,5-dimethylpyrazole	37.65	39.11	−0.24	0	−9.50	0.71	2.40	6.80
15	1,8-naphthyridine	43.45	36.93	−0.19	0	−9.90	0.55	1.86	10.35
16	1-adamantyl cyanide	38.15	36.98	−0.15	0	−10.79	0.79	2.75	7.93
17	1-butanethiol	24.05	27.68	−0.25	0.07	−11.38	0.78	0.69	0
18	1-cyclopropylethanone	37.45	35.49	−0.30	0	−11.57	0.74	2.25	6.24
19	1-methyl-4-(methylsulfonyl)-benzene	40.11	42.24	−0.94	0.05	−10.27	0.64	4.03	0
20	1-methylimidazole	40.25	36.84	−0.17	0	−10.25	0.65	2.82	6.62
21	1-methylpyrazole	34.35	37.91	−0.23	0	−9.68	0.65	2.08	7.08
22	1-propanesulfonic acid	36.61	35.23	−0.92	0.08	−12.38	0.60	3.69	0
23	1-propanethiol	22.55	26.47	−0.25	0.08	−11.41	0.77	0.67	0
24	2-propanol	32.35	34.23	−0.33	0	−11.95	0.83	1.17	5.46
25	2,2,2-trichlorethanol	30.45	30.50	−0.31	0	−11.85	0.27	2.16	4.76
26	2,2,2-trifluoroethanol	26.55	30.55	−0.31	0	−12.77	0.34	3.10	5.57
27	2,2,2-trifluoroethoxyethene	27.41	28.86	−0.24	0	−12.38	0.40	2.72	0
28	2,2,2-trifluoroethyl ether	29.23	27.84	−0.25	0	−13.01	0.23	4.07	0
29	2,2,2-trifluoroethyl methyl ether	29.63	29.76	−0.26	0	−12.71	0.44	3.56	0
30	2,2,2-trifluoroethyl trifluoroacetate	25.73	23.90	−0.27	0	−13.05	0.13	1.44	0
31	2,2-dimethyl-1-propanol	33.15	34.68	−0.33	0	−11.38	0.84	0.88	4.09
32	2,2-dimethylpropanenitrile	36.45	33.95	−0.21	0	−12.06	0.71	2.43	7.93
33	2,4,5-trimethylpyrazole	42.69	37.87	−0.18	0	−9.42	0.75	1.58	6.50
34	2,4-dimethyl-3-pentanone	37.55	35.98	−0.29	0	−11.68	0.83	2.33	5.95
35	2,5-dimethyltetrahydrofuran	35.05	33.84	−0.28	0	−11.39	0.90	1.36	0
36	2,6-difluoropyridine	33.23	32.68	−0.22	0	−11.31	0.38	3.04	4.94
37	2-butanone	36.05	35.36	−0.29	0	−11.94	0.80	2.38	6.24
38	2-ethoxy-2-methylpropane	35.45	33.28	−0.28	0	−11.41	0.92	0.84	0
39	2-fluoropyridine	35.19	33.23	−0.21	0	−11.00	0.46	2.47	5.29
40	2-methoxy-2-methylpropane	34.25	32.78	−0.28	0	−11.47	0.86	0.95	0
41	2-methyl-1-methylsulfanylpropane	27.41	31.48	−0.34	0.06	−10.68	0.91	0.28	0
42	2-methylpropane-1-thiol	23.75	27.85	−0.25	0.07	−11.22	0.77	0.59	0
43	2-methylpropane-2-thiol	23.85	28.29	−0.21	0.07	−11.00	0.80	0.84	0
44	2-methylpropanenitrile	35.75	32.97	−0.21	0	−12.29	0.66	2.38	7.85
45	2-propanethiol	22.45	26.78	−0.22	0.08	−11.11	0.76	0.77	0
46	1-propanol	31.45	34.53	−0.33	0	−11.81	0.83	1.12	5.68
47	3(5)-methylpyrazole	35.18	37.27	−0.23	0	−9.66	0.66	1.09	8.44
48	3,4,5-trimethylpyrazole	38.75	38.41	−0.17	0	−9.32	0.75	1.45	8.22
49	3-chloropyridine	31.65	32.94	−0.17	0	−10.86	0.65	1.10	5.29
50	3-methylpyridine	36.55	33.50	−0.18	0	−10.57	0.64	1.11	5.29
51	3-pentanone	36.75	35.60	−0.29	0	−11.78	0.80	2.37	6.24
52	4,4,4-trifluorobutylamine	37.15	33.29	−0.35	0	−12.18	0.55	2.85	4.20
53	4-fluorophenyl diphenylphosphinate	45.52	48.84	−1.16	0	−9.85	0.56	4.83	0
54	4-methylpyrazole	35.75	36.58	−0.17	0	−9.87	0.65	1.41	8.86
55	4-nitrophenyl methyl sulfone	35.91	36.32	−0.95	0.05	−11.51	0.35	3.35	0
56	4-trifluoromethylphenyl diphenylphosphinate	44.22	50.20	−1.16	0	−10.02	0.47	6.81	0
57	4-trifluoromethylpyridine	29.55	30.71	−0.16	0	−11.28	0.33	2.29	4.94
58	acetaldehyde	31.85	32.39	−0.29	0	−12.99	0.68	2.28	7.44
59	acetamide	39.82	40.86	−0.44	0	−10.84	0.68	3.21	10.69
60	acetic acid	32.73	33.22	−0.36	0	−12.35	0.57	2.30	5.99
61	acetone	35.35	33.39	−0.29	0	−12.72	0.71	2.56	6.87
62	acetonitrile	34.05	29.99	−0.15	0	−12.46	0.46	2.24	7.93
63	acetylacetone	43.13	40.88	−0.40	0	−10.64	0.69	3.04	11.46
64	ammonia	30.25	25.79	−0.40	0	−15.90	0.78	0.64	5.57
65	benzaldehyde	37.75	37.44	−0.29	0	−10.04	0.54	2.55	6.82
66	benzene	26.95	31.36	−0.13	0	−9.65	0.60	0	0
67	benzeneacetonitrile	35.15	35.31	−0.14	0	−9.92	0.49	2.24	7.61
68	benzenesulfonic acid, methyl ester	37.61	38.60	−0.95	0.05	−10.81	0.55	2.79	0
69	benzyl alcohol	35.85	36.81	−0.32	0	−9.79	0.64	1.04	5.41
70	bis(perfluoroisopropyl)ketone	21.93	20.23	−0.14	0	−13.46	0	0.03	4.85
71	bis-difluoromethyl ketone	24.63	25.01	−0.18	0	−13.46	0.19	1.69	6.69
72	bis-trifluoromethylmethanol	23.83	26.30	−0.28	0	−13.34	0.14	2.42	4.76
73	bromocyanide	29.41	35.14	−0.27	0	−11.92	0.80	1.97	7.93
74	butanenitrile	35.45	33.19	−0.21	0	−12.12	0.63	2.40	7.85
75	carbonic acid, dimethyl ester	37.05	34.18	−0.34	0	−11.67	0.64	3.27	0
76	carbonyl fluoride	18.43	23.48	−0.28	0	−13.97	0.07	0.91	7.52
77	chloroacetonitrile	29.45	28.59	−0.16	0	−12.19	0.24	1.94	8.01
78	chloroformic acid methyl ester	28.93	31.43	−0.31	0	−12.17	0.71	1.76	0
79	cyanobenzene	35.55	34.85	−0.14	0	−10.18	0.41	2.72	7.93
80	cyclohexanemethanol	34.35	36.61	−0.33	0	−11.07	0.86	1.33	5.78
81	dichloroacetonitrile	27.73	28.58	−0.17	0	−12.36	0.35	1.45	7.77
82	dicyanomethane	26.33	29.17	−0.15	0	−13.29	0.24	2.20	16.02

TABLE 1 (Continued)

no.	compound	LCB(exp)	LCB(pred)	q_{min}	*N*s	HOMO-1	FPSA-1	u_{c}	HASA-2
83	dicyclopropyl-methanone	38.45	35.20	−0.31	0	−11.45	0.76	1.86	5.32
84	diethyl chloromethylphosphonate	44.15	44.01	−1.07	0	−11.48	0.67	3.66	0
85	diethyl methylphosphonate	44.92	45.34	−1.09	0	−11.33	0.80	3.43	0
86	diethyl sulfide	26.45	29.50	−0.27	0.07	−10.87	0.95	0.06	0
87	diisopropyl ether	35.55	33.85	−0.28	0	−11.12	0.89	1.02	0
88	diisopropyl phosphonate	44.02	42.34	−1.10	0	−11.47	0.77	1.45	0
89	diisopropyl sulfide	28.95	30.81	−0.21	0.05	−10.49	0.93	0.25	0
90	dimethyl ether	29.55	30.63	−0.28	0	−12.29	0.79	1.05	0
91	dimethyl formamide	41.55	39.60	−0.37	0	−10.85	0.75	3.15	8.13
92	dimethyl methylphosphonate (dmmp)	43.92	41.74	−1.12	0	−11.55	0.74	1.08	0
93	dimethyl phosphite	42.42	40.15	−1.09	0	−11.77	0.59	1.49	0
94	dimethyl sulfate	33.91	34.28	−0.94	0.08	−12.17	0.59	2.59	0
95	dimethyl sulfide	23.45	27.07	−0.35	0.11	−11.03	0.91	0.01	0
96	dimethylacetamide	42.85	40.05	−0.37	0	−10.73	0.77	3.17	7.98
97	dimethylamine	32.15	31.58	−0.31	0	−12.48	0.88	0.34	3.49
98	dimethylcyanamide	39.05	32.37	−0.17	0	−12.72	0.58	2.75	10.48
99	dimethyl sulfoxide	41.71	38.09	−0.78	0.10	−10.95	0.77	4.97	0
100	di-*n*-butyl sulfide	30.65	31.41	−0.27	0.04	−10.91	0.96	0.11	0
101	di-*n*-propyl ether	34.85	33.53	−0.28	0	−11.35	0.93	0.83	0
102	diphenyl sulfone	40.51	42.04	−0.94	0.04	−10.16	0.54	4.01	0
103	diphenyl sulfoxide	43.81	41.46	−0.79	0.04	−9.84	0.59	4.19	0
104	dipropyl sulfide	28.95	30.55	−0.27	0.05	−10.91	0.94	0.08	0
105	di-*tert*-butyl sulfide	31.15	31.13	−0.21	0.04	−10.35	0.88	0.07	0
106	ethanol	30.45	33.22	−0.33	0	−12.33	0.81	1.12	5.57
107	ethoxyethane	33.35	32.38	−0.28	0	−11.76	0.89	0.86	0
108	ethyl acetate	36.05	34.46	−0.36	0	−11.35	0.78	1.92	0
109	fluoroacetonitrile	26.21	27.35	−0.19	0	−13.21	0.29	2.06	7.93
110	formaldehyde	25.45	28.37	−0.28	0	−14.54	0.63	2.02	7.68
111	formamide	37.52	40.34	−0.45	0	−10.94	0.63	3.11	11.18
112	formic acid ethyl ester	33.95	34.54	−0.30	0	−11.67	0.67	3.81	0
113	formic acid methyl ester	32.45	32.04	−0.35	0	−11.64	0.63	1.53	0
114	formic acid *n*-butyl ester	34.35	35.58	−0.30	0	−11.52	0.74	3.92	0
115	formic acid *n*-propyl ester	34.35	35.35	−0.30	0	−11.52	0.71	3.88	0
116	glycol sulfate	32.91	33.05	−0.91	0.09	−12.58	0.47	3.89	0
117	glycol sulfite	35.51	29.61	−0.34	0.08	−10.91	0.95	0.24	0
118	heptylcyanide	36.81	35.56	−0.21	0	−11.57	0.76	2.51	8.01
119	hexafluoroacetone	19.13	17.71	−0.14	0	−15.31	0.02	0.48	6.51
120	hexafluoroacetylacetone	27.33	30.01	−0.33	0	−12.03	0.10	1.37	10.97
121	hexafluoro-diacetamide	35.23	30.32	−0.36	0	−12.47	0.07	1.54	13.41
122	hexamethylphosphoramide	47.42	49.54	−1.15	0	−9.91	0.87	3.48	0
123	hydrogen cyanide	25.95	24.66	−0.19	0	−13.67	0.16	1.49	7.93
124	imidazole	38.15	35.42	−0.21	0	−10.67	0.58	2.13	8.22
125	isobutanol	32.55	35.25	−0.33	0	−11.37	0.86	1.01	4.89
126	isooxazole	32.91	29.85	−0.23	0	−11.31	0.43	1.63	0
127	isophorone	41.51	40.29	−0.30	0	−10.32	0.78	3.55	6.99
128	methanesulfonic acid, methyl ester	36.22	33.50	−0.97	0.08	−12.03	0.61	1.53	0
129	methanethiosulfonic acid, methyl ester	36.32	30.87	−0.96	0.17	−10.64	0.55	1.54	0
130	methanol	28.55	32.28	−0.33	0	−12.50	0.70	1.14	6.46
131	methoxyacetonitrile	32.85	32.52	−0.26	0	−12.64	0.52	3.02	7.93
132	methoxybenzene	30.21	33.66	−0.21	0	−9.77	0.65	0.89	0
133	methoxyethanol	42.65	34.72	−0.33	0	−11.09	0.77	0.52	5.68
134	methyl acetate	35.25	33.36	−0.35	0	−11.51	0.70	1.84	0
135	methyl dimethylcarbamate	39.95	35.80	−0.40	0	−11.35	0.77	2.23	1.75
136	methyl phenyl sulfone	39.31	39.71	−0.94	0.06	−10.66	0.56	3.58	0
137	methyl sulfone	37.01	33.03	−0.95	0.09	−12.59	0.62	2.56	0
138	methyl thiolacetate	33.85	33.45	−0.36	0.09	−10.54	0.78	2.44	6.24
139	methyl trifluoroacetate	28.95	28.52	−0.28	0	−12.37	0.32	2.65	0
140	methylacetamide	41.42	40.77	−0.39	0	−10.78	0.71	3.60	9.50
141	methylamine	31.35	32.22	−0.35	0	−12.47	0.83	0.47	4.55
142	methyl-phenyl-phosphinic acid methyl ester	45.02	47.71	−1.13	0	−10.55	0.64	4.85	0
143	methylthioacetonitrile	34.35	30.07	−0.36	0.10	−11.48	0.63	2.24	8.01
144	methylthioethane	25.05	29.61	−0.34	0.08	−10.91	0.95	0.24	0
145	*N*,*N*-dimethyl cyanoformamide	34.51	40.14	−0.32	0	−11.72	0.72	3.62	15.76
146	*N*,*N*-dimethyl-3-pyridinamine	38.69	36.88	−0.24	0	−10.21	0.70	1.59	7.64
147	*N*,*N*-dimethyl-4-pyridinamine	42.05	38.29	−0.25	0	−9.84	0.71	2.05	7.20
148	*N*,*N*-dimethyltrifluoroacetamide	39.71	36.10	−0.31	0	−11.51	0.45	4.09	7.56
149	*n*-butanal	33.35	35.93	−0.29	0	−11.73	0.77	2.44	7.36
150	*n*-butanol	32.85	35.39	−0.33	0	−11.43	0.84	1.12	5.68
151	*n*-butyl ether	36.55	33.72	−0.28	0	−11.23	0.93	0.79	0
152	*n*-heptanal	34.61	37.26	−0.29	0	−11.34	0.82	2.52	7.36
153	*n*-hexanal	34.41	37.01	−0.29	0	−11.42	0.81	2.50	7.44
154	*N*-methylformamide	39.65	40.32	−0.40	0	−10.91	0.69	3.51	9.35
155	octylcyanide	37.55	35.78	−0.21	0	−11.47	0.76	2.52	8.09
156	pentanal	33.81	36.55	−0.29	0	−11.54	0.79	2.48	7.40
157	perfluoropyridine	22.33	26.00	−0.15	0	−11.27	0.10	0.18	4.94
158	perfluoro-*tert*-butyl alcohol	20.33	22.84	−0.26	0	−13.61	0.05	1.07	4.23
159	perfluoro-*tert*-butylcarboxylic acid ethyl ester	34.53	28.32	−0.28	0	−12.62	0.28	3.13	0
160	perfluoro-*tert*-butylamine	23.83	25.71	−0.34	0	−13.53	0.12	2.20	3.31
161	phenyl diphenylphosphinate	46.82	48.04	−1.16	0	−9.52	0.60	3.34	0
162	phenyl methyl sulfoxide	42.81	41.31	−0.78	0.06	−9.92	0.65	4.60	0
163	phosphoryl chloride	34.71	29.11	−0.83	0	−13.12	0.02	1.19	0

TABLE 1 (Continued)

no.	compound	LCB(exp)	LCB(pred)	$q_{\min}$	Ns	HOMO-1	FPSA-1	u_c	HASA-2
164	propanal	32.85	34.78	−0.29	0	−12.11	0.74	2.39	7.32
165	propanoic acid, 2,2-dimethyl-, ethyl ester	38.93	35.51	−0.35	0	−11.19	0.85	2.01	0
166	propanoic acid, methyl ester	36.35	35.38	−0.30	0	−11.47	0.71	3.88	0
167	propionitrile	35.35	31.87	−0.21	0	−12.52	0.59	2.32	7.93
168	pyrazine	28.65	32.28	−0.12	0	−10.40	0.51	0	9.87
169	pyrazole	33.65	36.48	−0.23	0	−9.93	0.55	1.48	8.96
170	pyridazine	41.45	34.56	−0.14	0	−10.78	0.52	1.91	11.04
171	pyridine	35.05	32.61	−0.18	0	−10.65	0.58	0.92	4.94
172	pyrimidine	29.85	34.55	−0.23	0	−10.62	0.55	0.98	9.36
173	*sec*-butyl alcohol	33.35	35.09	−0.33	0	−11.49	0.87	1.06	4.70
174	silane	34.63	38.09	−0.62	0	−10.91	0.88	0.97	0
175	*S*-methyl trifluoroacetothioate	29.93	31.24	−0.37	0.09	−11.29	0.43	4.13	6.14
176	sulfur dioxide	18.23	19.42	−0.73	0.33	−12.38	0.46	5.93	0
177	*tert*-butyl alcohol	33.31	34.57	−0.33	0	−11.77	0.84	1.18	5.24
178	tetrahydro-2-methylfuran	34.35	33.76	−0.28	0	−11.38	0.88	1.45	0
179	tetrahydrofuran	32.75	33.76	−0.28	0	−11.40	0.87	1.54	0
180	tetrahydrothiophene	25.85	29.59	−0.26	0.08	−10.98	0.97	0.71	0
181	tetrahydrothiopyran	25.95	31.13	−0.27	0.06	−10.63	0.99	0.47	0
182	tetramethylene sulfone	38.91	36.69	−0.93	0.07	−11.94	0.70	2.93	0
183	tetramethylene sulfoxide	43.01	40.45	−0.77	0.07	−10.74	0.82	4.83	0
184	tetramethylguanidine (tmg)	42.45	38.74	−0.26	0	−9.69	0.84	1.13	7.47
185	tetrazole	33.38	36.17	−0.22	0	−12.13	0.32	3.30	21.04
186	thiazole	33.45	31.49	−0.45	0.13	−10.55	0.64	2.68	5.63
187	thioethanol	21.45	24.58	−0.25	0.11	−11.37	0.74	0.63	0
188	thiomethanol	20.35	20.61	−0.32	0.17	−11.51	0.62	0.41	0
189	trichloroacetaldehyde	27.25	29.13	−0.21	0	−12.27	0.35	1.55	6.95
190	trichloroacetonitrile	26.81	26.04	−0.17	0	−12.62	0.23	0.54	7.93
191	triethyl phosphate	45.02	42.47	−1.09	0	−11.41	0.83	1.13	0
192	triethylphosphine oxide	46.62	46.84	−1.16	0	−10.54	0.88	2.21	0
193	trifluoroacetaldehyde	21.83	23.38	−0.19	0	−14.80	0.18	2.39	7.20
194	trifluoroacetamide	33.95	35.01	−0.41	0	−11.72	0.24	3.27	10.35
195	trifluoroacetic acid ethyl ester	30.65	30.57	−0.28	0	−12.10	0.43	3.05	0
196	trifluoroacetonitrile	21.33	22.76	−0.21	0	−14.65	0.28	0.58	7.93
197	trifluoromethyl disulfide	19.23	14.46	−0.16	0.20	−10.66	0.20	0.01	0
198	trifluoromethylacetylene	17.91	26.46	−0.27	0	−12.57	0.11	2.83	0
199	trimethyl phosphate	43.75	48.26	−1.01	0	−11.39	0.72	7.17	0
200	trimethylamine	32.05	30.85	−0.27	0	−12.39	0.88	0.18	2.70
201	trimethylphosphine oxide	45.62	47.40	−1.16	0	−10.55	0.80	3.15	0
202	triphenyl phosphate	45.12	46.04	−1.04	0	−9.55	0.56	3.14	0
203	triphenylphosphine oxide	47.42	47.60	−1.20	0	−9.87	0.62	3.06	0
204	valeronitrile	35.85	33.62	−0.21	0	−12.10	0.67	2.44	8.01
205	water	24.77	26.99	−0.38	0	−14.95	0.56	1.09	7.57

polarized diffuse split-valence basis sets are required to reproduce quantitatively the experimentally measured LCA values.[39] Recent papers by Remko[40,41,43] and Alcami et al.[32] indicate that limited sets of small bases treated by the G1, G2(MP2), G2, and CBS-Q methods[44−47] all yield LCAs within so-called chemical accuracy (about 2 kcal/mol).

High-level calculations are needed for predictions of LCBs (e.g. G2 level), and even then, some empirical correction is needed to refine absolute LCB values.[48]

A revised, re-anchored, widened, and consistent LCB scale was recently published by Burk et al.[48] This scale contains LCBs for 205 compounds and covers the lithium basicity range from 17.9 (trifluoromethylacetylene) to 47.4 (triphenylphosphine oxide) kcal/mol. In the current study, we attempt to correlate gas-phase lithium cation basicities with theoretical descriptors, calculated solely from molecular structure using a quantitative structure−property relationship (QSPR) technique.

Data Set and Methodology

The methodology for a general QSPR approach has been developed and coded as the CODESSA PRO[49] software, which combines different ways of quantifying the structural information about a molecule with advanced statistical analyses for the establishment of molecular structure−property relationships. CODESSA can calculate a large number of quantitative descriptors solely on the basis of molecular structural information.[50,51] CODESSA PRO has been applied successfully to predict a variety of physical properties of compounds.[52−55]

Experimental lithium cation basicity (LCB) values for the 205 organic molecules (Table 1) were taken from the literature.[48] The structures were drawn using ISIS Draw 2.4[56] and preoptimized using the molecular mechanics force field method (MM+) available in HyperChem 7.0.[57] Final geometrical optimization was performed with a cloned version of MOPAC 7.0,[58] as implemented in the CODESSA PRO software using the AM1[59] semiempirical method. Thereafter, CODESSA PRO was used to calculate five types of molecular descriptors: constitutional, topological, geometrical, electrostatic, and quantum-chemical.[50,60] The constitutional and topological descriptors were calculated from the 2D structure of the free-base molecules. The geometrical, electrostatic, and quantum chemical descriptors were obtained using the AM1 optimized geometry and wave function of the free-base molecules. Altogether, 1042 descriptors were calculated for each of the 205 compounds studied. The correlation analysis to find the best QSPR model was carried out using the BMLR (best multilinear regression) method in CODESSA PRO. The best multilinear regression method is based on the (i) selection of the orthogonal descriptor pairs and (ii) extension of the correlation (saved on the previous step) with the addition of new descriptors until the Fisher-criterion (F)[61] becomes less than that of the best two-parameter correlation. The best N correlations (by R^2) are saved.

Experimental and calculated LCB values and corresponding descriptors are listed in Table 1.

Results and Discussion

To find the optimum number of descriptors[54,62] describing the lithium cation basicities (LCB) for the current set of structures, we analyzed multiparameter correlations containing up to 10 descriptors. Figure 1 shows the relationships of R^2 and

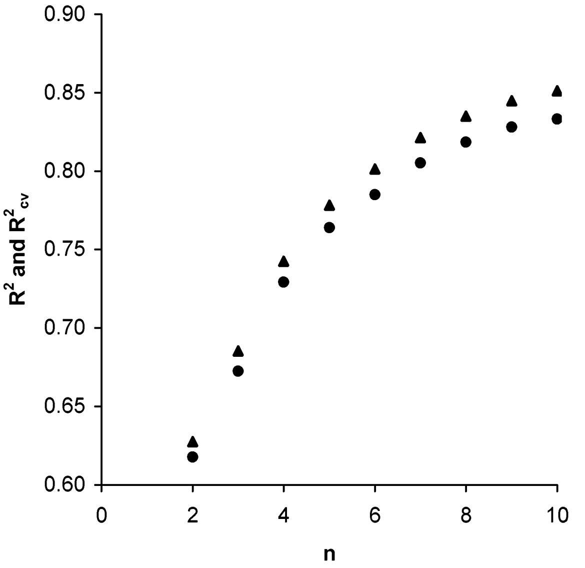

Figure 1. Number of parameters (*n*) plotted vs R^2 (▲) and R^2_{cv} (●) values.

TABLE 2: The Six-Parameter Model for Lithium Cation Basicities[a]

no.	coefficient	*t*-test	descriptor
0	44.78 ± 2.87	15.61	intercept
1	−11.85 ± 0.98	−12.14	minimum net atomic charge
2	−59.44 ± 5.36	−11.08	relative number of S atoms
3	2.07 ± 0.20	10.21	HOMO-1 energy
4	8.35 ± 1.08	7.77	FPSA-1 fractional PPSA (PPSA-1/TMSA) (MOPAC PC)
5	1.25 ± 0.19	6.54	total point-charge component of the molecular dipole
6	0.33 ± 0.06	5.41	HASA-2 (MOPAC PC)

[a] $R^2 = 0.801$; $R^2_{cv} = 0.785$; $F = 133.11$; $s^2 = 8.78$; $N = 205$, where R^2 is the squared correlation coefficient, R^2_{cv} is the squared cross-validated correlation coefficient, *F* is the Fisher criterion, s^2 is the squared standard error, and *N* is the number of data points.

R^2_{cv} with the number of descriptors. As it can be seen in Figure 1, R^2 and R^2_{cv} rise steeply as the number of parameters increases from 2 to 10. To avoid the "over-parametrization" of the model, an increase of the R^2 value of less than 0.02 was chosen as the breakpoint criterion. Therefore, we used the best correlation equation with six descriptors for the analysis (Table 2, eq 5). The plot of observed vs predicted LCB values is illustrated in Figure 2.

The descriptors in Table 2 are sorted by the *t*-test. The value of the descriptor's coefficient cannot be treated as an indicator of the importance of the descriptor in an equation as the absolute numeric values of the descriptors vary in a large range (the descriptors are not normalized). Thus, the *t*-test values for each descriptor have been used for this purpose. The regressor variables with larger *t*-test absolute values are considered statistically more significant in the description of the property (LCB). Table 2 represents a linear combination of the six descriptors for the LCB values and can also be presented as shown in eq 5.

$$\begin{aligned}\mathrm{LCB} = (44.78 \pm 2.87) - (11.85 \pm 0.98)q_{\min} - \\ (59.44 \pm 5.36)N_S + (2.07 \pm 0.20)\text{HOMO-1} + \\ (8.35 \pm 1.08)\text{FPSA-1} + (1.25 \pm 0.19)\mu_c + \\ (0.33 \pm 0.06)\text{HASA-2} \quad (5)\end{aligned}$$

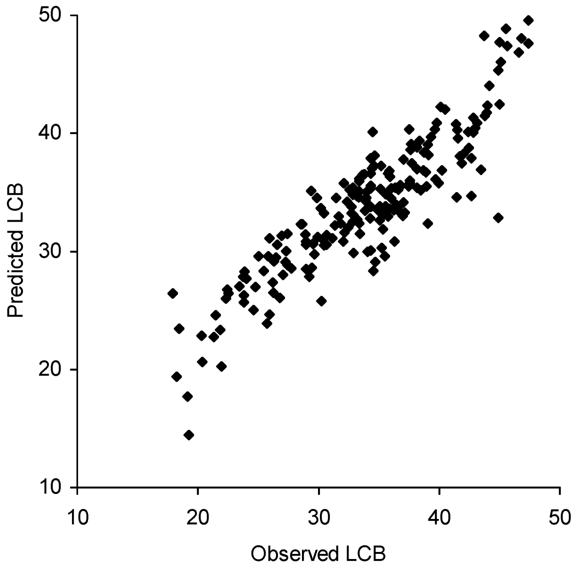

Figure 2. Plot of observed vs predicted LCB (kcal/mol).

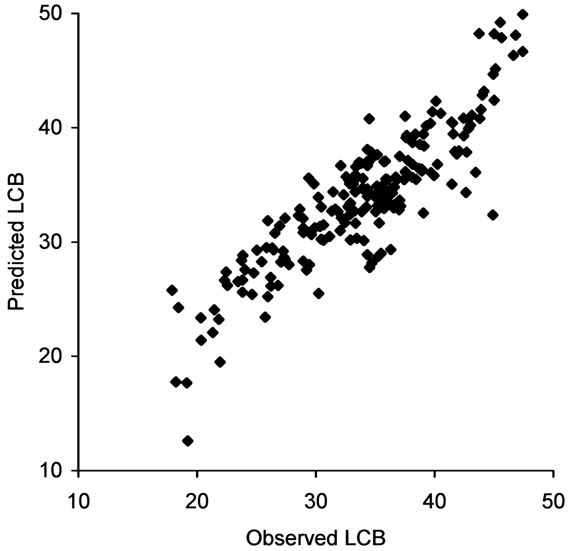

Figure 3. Cross-validation plot for the six-parameter model.

The first descriptor in Table 2 (and in eq 5) is *the minimum net atomic charge* (or *the maximum negative atomic charge*, $q_{\min}$), which, presumably, contributes to the intensity of the general electrostatic, in particular the Coulombic, interactions. It is logically the most important descriptor as Li^+ forms highly ionic bonds with bases.[25−32] The $q_{\min}$ is also related to the hydrogen-bonding (HB) ability of a molecule because a high positive value on hydrogen atoms implies good HB donor propensity, whereas a high negative value on heteroatoms (N, O, F, S, and P) implies good acceptor ability of these atoms.

The second descriptor, *the relative number of sulfur atoms* (N_S), is defined as the ratio of the number of sulfur atoms to the total number of non-hydrogen atoms in the base. Its importance in the current model can be rationalized as a measure of the local polarizability—the sulfur atom has a relatively large radius and is easily polarizable, especially in thiols and thioalcohols. The N_S descriptor can be considered as closely related to the third descriptor—*the HOMO-1 energy*. The HOMO-1 energy reflects the reactivity and polarizability of the molecule. Li^+ has a relatively small radius and thus a high polarizing power. The polarizability of base should influence significantly the strength of the Li^+−B bond.

The fourth descriptor is *the fractional charged partial surface area* (FPSA-1), calculated from MOPAC, based on Mulliken charges. This charge distribution-related descriptor is defined

TABLE 3: Intercorrelation of the Descriptors (R^2 Values)

	N_s	FPSA-1	HASA-2	HOMO-1	μ_c	q_{min}
N_s	1	0.0056	0.1158	0.0070	0.0017	0.0497
FPSA-1	0.0056	1	0.0712	0.2072	0.0275	0.0097
HASA-2	0.1158	0.0712	1	0.0114	0.0001	0.2125
HOMO-1	0.0070	0.2072	0.0114	1	0.0066	0.0264
μ_c	0.0017	0.0275	0.0001	0.0066	1	0.2079
q_{min}	0.0497	0.0097	0.2125	0.0264	0.2079	1

TABLE 4: Validation of the Six-Parameter Model

training sets	R^2 (fit)	s^2 (fit)	predicted sets	R^2 (pred)	s^2 (pred)
B + C	0.789	7.245	A	0.817	5.994
A + C	0.802	7.087	B	0.789	8.909
A + B	0.829	6.383	C	0.732	9.860
average	0.807	6.905	average	0.779	8.254

as a ratio of the charged partial surface area (PPSA-1) and the total molecular surface area (TMSA)[63] and provides a measure of the polarity of a compound.

The fifth descriptor, *the total point-charge component of the molecular dipole* (μ_c), is also charge related; it reflects polarizability and is related to the molecular bulk or molar volume. Together with the FPSA-1 descriptor, μ_c once more underlines the importance of ionic interaction between the lithium cation and the base.

The final descriptor in Table 2 is HASA-2 (*the area-weighted surface charge of a hydrogen-bonding acceptor atom*). HASA-2 is defined by eq 6, and describes the hydrogen-bonding acceptor ability of the molecule.[60]

$$\text{HASA-2} = \sum_{A} \frac{q_A \sqrt{S_A}}{\sqrt{S_{tot}}} \qquad (6)$$

In eq 6, q_A is the partial charge on the hydrogen-bonding donor (H) atom(s), S_A is the surface area for this atom, and S_{tot} is the total molecular surface area.

Descriptors' Intercorrelation

A major challenge in the development of multiple regression equations is connected with the possible multicollinearity of molecular descriptor scales. In the case of high mutual correlation of the descriptors, the overall statistical characteristics of the regression may be satisfactory, but the reliability of the descriptors' coefficients, and thus of the whole regression, is low. The multicollinearity can be avoided, at least in part, by examining the correlation coefficients between the descriptors' scales in the QSPR model.[60] In Table 3 we have listed the correlation coefficients between the descriptors' scales, which were involved in the current six-parameter model. Table 3 demonstrates that all the descriptors are strongly orthogonal, which reflects the statistical reliability of the model.

Validation

To demonstrate the absence of chance correlations, we used the internal validation method. The full set of 205 structures was divided into three groups: structures 1, 4, 7, etc. formed group A, structures 2, 5, 8, etc. formed group B, and structures 3, 6, 9, etc. formed group C. Each subset was predicted by using the other two subsets as the training set. In this procedure, the same descriptors were retained in the correlation equation, but the coefficients were allowed to vary. Similar methods have been used elsewhere.[55,64−66] The results shown in Table 4 disclose an average training quality of $R^2 = 0.807$ and an average predicting quality of $R^2 = 0.779$, which demonstrates that the proposed model has a satisfactory statistical stability and validity. The correlation chart of the validation showing the summary of all three predictions is given in Figure 3.

Conclusions

The gas-phase lithium cation basicity (LCB) for a diverse set of 205 compounds was satisfactorily described with the six-parameter QSPR model. All the descriptors involved were calculated solely from the chemical structures and have a definite physical meaning corresponding to different intermolecular interactions. Statistical validation of the model demonstrated that the proposed model has a normal statistical stability and validity.

Our model also confirms the electrostatic nature of the lithium cation−base interaction, as the minimum net atomic charge, the HOMO-1 energy, the FPSA-1, the total point-charge component of the molecular dipole, and the HASA-2 are directly charge-related descriptors.

Acknowledgment. Part of this work was supported by the ETF Grant no. 5196.

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