

Lewis Acids in Organic Synthesis. Approach to a Selection Strategy for Screening Experiments

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A computer-assisted strategy for selecting suitable Lewis acid catalysts in organic synthesis is described. The strategy is based on principal components (PC) analysis of measured Lewis acid properties. A two-component model accounts for 65 % of the variation in a set of 20 descriptors for 116 different Lewis acids. PC-eigenvector projections of the data allow for a systematic search of test candidates in screening experiments. The strategy is demonstrated by experimental studies on 3 Lewis acid-catalyzed reactions: alkylation of silyl enol ether, Diels-Alder reaction, and Friedel-Crafts acylation.

Electrophilic catalysis by Lewis acids is essential in a number of important synthesis reactions. When a newly discovered reaction is to be elaborated into a useful synthetic procedure, an early and important step is to establish a suitable reaction system which can be optimized. With Lewis acid-catalyzed reactions, this implies the selection of suitable catalysts. However, this is not a trivial problem. With new reactions, mechanistic details are still obscure and it is not likely that such details will be revealed before the preparative utility of the reaction has been demonstrated. This means that a selection of catalysts for experimental studies will precede a detailed study of the reaction mechanism.

Although great effort has been spent on theoretical as well as empirical studies of Lewis acids,¹ no general agreement has yet been reached on how to define "acidity" of Lewis acids. The rather fuzzy concept of hard/soft acids and bases further complicates the picture.² This strongly indicates that it is not possible to use a single measured property as a probe of Lewis acidity. To achieve a satisfactory quantitative description, it is likely that several factors must be jointly considered and different multiparameter models have been suggested.¹ However, these models depend on theoretical *a priori* assumptions which may or may not apply to the current

synthetic problem. A modest but reasonable assumption is that Lewis acids, which are similar to each other with regard to various measured properties, may also show a similarity in behaviour when they take part in a chemical reaction. By this is meant that macroscopic properties are likely to be manifestations of intrinsic properties of the Lewis acids and that the same intrinsic properties are also responsible for the chemical reactivity. It certainly does not mean that chemical reactivity can be "explained" in a philosophical sense by the macroscopic properties. What is assumed is that macroscopic properties can be used as probes of intrinsic properties.

A number of physical and chemical properties can be used to characterize Lewis acids. Data on bulk properties and thermodynamic parameters can be compiled from various sources for a large number of acids. In the developmental phase of a new synthetic method it is not known with certainty *which* properties will be important for a catalytic effect. It is therefore desirable that a selection of test candidates for screening experiments cover a broad range of acid properties. However, it is impossible or at least very difficult to make such a selection from a huge table by mere inspection. In a recent paper³ we discussed a similar problem – selection of solvents, and how a computer-assisted strategy based on multi-

variate statistical analysis can be used to reduce the complexity of the problem. In this paper, we extend these principles to the selection of Lewis acids. The methods have been described in detail³ so we do not repeat the discussion here.

Results

Initial study In an initial study, a set of 10 property descriptors for 28 Lewis acids, Table 1, was subjected to a principal components (PC) analysis. A two-component PC model was significant

according to cross validation and accounted for 54% of the variation in the descriptors. The result is illustrated by the PC projection in Fig. 1 (a). The important point is that the *systematic* variation in the original data set can be described by only two descriptors t_1 and t_2 . The extent to which each of the original descriptors contributes to the principal components t_1 and t_2 is shown in the loading plot in Fig. 1 (b).

The PC projection can be used to select test candidates for a screening experiment. A thorough discussion of various selection strategies is given in Ref. 3. Here, it will be sufficient to say that acids which are well separated from each

Table 1. Lewis acid descriptors^a for a preliminary study

Acids	1	2	3	4	5	6	7	8	9	10
1 AlCl ₃	2.1	704.2	628.8	110.47	91.84	2.26	102	15.8	12.01	—
2 BF ₃	0	1137	1120.33	254.12	50.46	1.295	154	3.9	15.5	—
3 MoS ₂	—	235.1	225.9	62.59	63.55	—	—	—	—	—
4 SnCl ₄	0	511.3	440.1	258.6	165.3	2.43	7.6	2.87	—	-115
5 SO ₂	1.63	320.5	—	237.6	—	1.4321	119	15.4	12.34	-18.2
6 POCl ₃	2.4	519.1	520.8	222.46	138.78	1.95	122	13.3	11.89	-67.8
7 Me ₃ B	—	143.1	32.1	238.9	—	1.56	89	—	10.69	—
8 Me ₃ Al	—	136.4	99	209.41	155.6	—	61	2.9	9.76	—
9 Me ₂ SnCl ₂	3.56	336.4	—	—	—	2.37	—	—	10.43	—
10 TiO ₂	—	913.4	853.9	56.3	9.96	1.97	160	48	10.2	0
11 ZnCl ₂	2.12	415.05	369.39	111.46	71.34	2.32	96	—	12.9	-65
12 TiCl ₃	—	720.9	653.5	139.7	97.2	2.138	110	—	—	1110
13 TiCl ₄	0	804.2	737.2	252.3	145.2	2.19	181	2.8	11.76	-54
14 VCl ₄	0	576.8	503.27	242.44	—	2.03	92	—	—	1130
15 CrCl ₂	—	395.2	356.1	114.5	71.1	2.12	91	—	9.97	6890
16 MnCl ₂	—	481.3	440.3	118.2	72.9	2.32	98.8	—	11.02	14350
17 FeCl ₂	—	341.79	302.3	117.95	76.65	2.38	95	—	10.34	14750
18 FeCl ₃	1.28	404.6	398.3	146.4	128	2.32	81	—	—	—
19 CoCl ₂	—	325.2	282.2	106.5	78.5	2.53	86	—	10.6	12660
20 NiCl ₂	3.32	305.332	259.032	97.65	71.67	—	87	—	11.23	6145
21 CuCl ₂	—	220.1	175.1	108.07	71.88	—	91.5	—	—	1080
22 GaCl ₃	0.85	524.17	454.36	172	—	2.208	78.7	—	11.96	-63
23 GeCl ₄	0	543.4	—	347.15	29.21	2.1	81	2.43	11.68	-72
24 AsCl ₃	1.53	335.24	294.7	233.2	—	2.16	70	1.59	11.7	-79.9
25 BCl ₃	0.61	427.2	387.4	206.3	106.7	1.75	109	0	11.62	-59.9
26 SiCl ₄	0	601.54	569.32	328.6	145.17	2.019	95.3	2.4	12.06	-88.3
27 SbCl ₃	3.9	381.75	324.1	186	107.84	2.325	74	33	10.75	-86.7
28 PCl ₃	7.8	314.7	272.3	217.1	—	1.95	78.5	3.43	9.91	—

^aThe values were compiled from standard reference handbooks. The data may differ from values given in Table 3 which were compiled from much more complete background material. The calculations in the preliminary study were carried out using the data given in Table 1. Descriptors: 1, dipole moment (vapour phase) (D); 2, negative of standard enthalpy of formation (kJ mol⁻¹); 3, negative of standard Gibbs energy of formation (kJ mol⁻¹); 4, standard entropy (J mol⁻¹ K⁻¹); 5, heat capacity (J mol⁻¹ K⁻¹); 6, mean bond length (Å); 7, mean bond energy (kcal mol⁻¹); 8, dielectric constant; 9, ionization potential (eV); 10, magnetic and diamagnetic susceptibility (10⁻⁶ cgs).

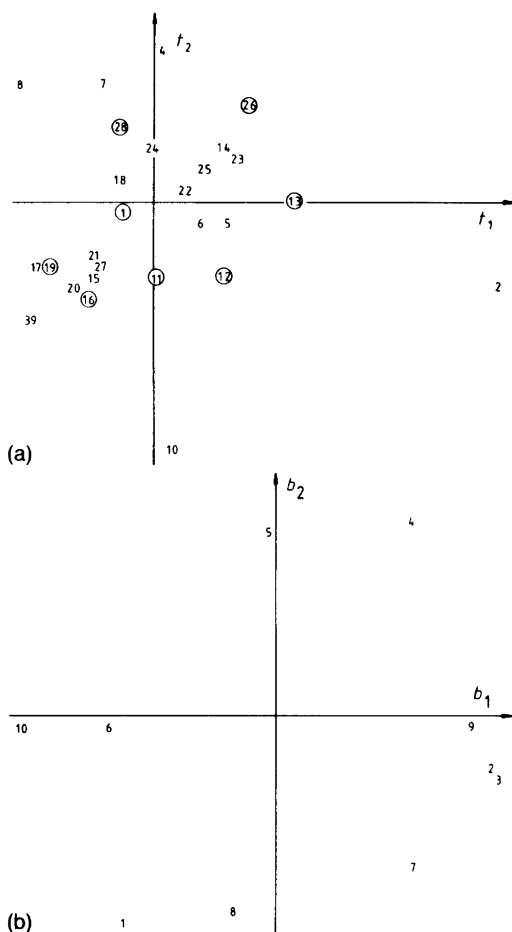


Fig. 1. (a) PC projections of descriptors in the preliminary study. (b) Loadings in the PC model. Loadings along the b_1 axis contribute to the t_1 component.

other and which have a broad distribution over the projection are obvious candidates for testing.

Experimental evaluation. A subset of 9 different Lewis acids was selected from the PC projection (encircled numbers in Fig. 1 (a)). The selected acids were used as catalysts in three reactions: A, *Reetz* alkylation of silyl enol ethers⁴; B, *Diels-Alder* reaction; and C, *Friedel-Crafts* acylation. The specific reactions studied are shown in Scheme 1. The results obtained in these experiments are shown in Table 2. It was difficult to measure the initial rates of the reactions. As another, albeit

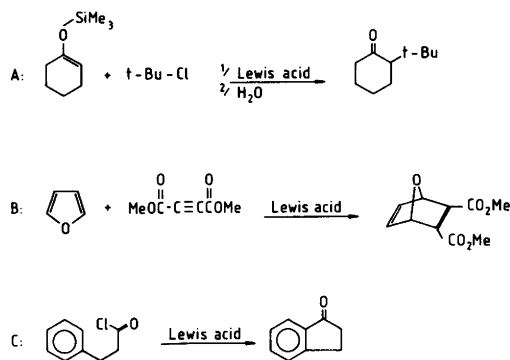
rather rough, measure of the reactivity, we used t_{50} which was defined as the time necessary to obtain 50% of the final yield.

Augmented study. The results of the initial study and the experimental evaluation were promising enough to justify an augmented study of Lewis acid descriptors, therefore, a set of 20 descriptors for 116 Lewis acids (MX_n , X = F, Cl, Br, I) was compiled from various sources (see Table 3). A two-component PC model accounts for 65% of the variation in Table 3. Inclusion of a third component did not improve the explained variance and was insignificant according to cross validation. The results of the PC analysis are shown in Figure 2.

Strategies for selection

The PC projections of the Lewis acids, Fig. 1 (a) and 2 (a) show the *systematic* variation in all the properties considered in Tables 1 and 3. We can use this information for a systematic search for test candidates. A subset of all the possible candidates can be selected in such a way that a suitable spread in all properties is assured. As with the selection of solvents discussed in a previous paper³, we can envisage several ways to proceed:

- (1) *Dissimilar acids*: Select acids which are found on the periphery of the plot and placed far from each other. This will give a selection in which the dissimilarities are maximized.
- (2) *Uniform coverage*: Select acids that are uniformly spread with regard to properties. This can



Scheme 1. Reactions used in screening experiments.

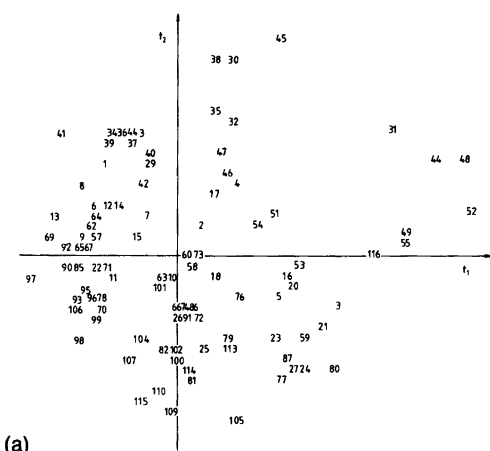
be done by selecting candidates that form a regular lattice in the projection.

(3) *Sequential simplex search*: A sequential simplex strategy¹⁴ can be used to achieve a systematic search for a suitable catalyst. For this, the more complete projection in Fig. 2 (a) is preferable. The simplex search can be performed by selecting 3 acids near the center of the projection in such a way that their points form an approximately equilateral triangle in the projection. (If some acids are *known* to be useful, these are, of course, included in the initial simplex.) Run the experiments and determine the poorest candidate of the 3, discard it and replace it with a new can-

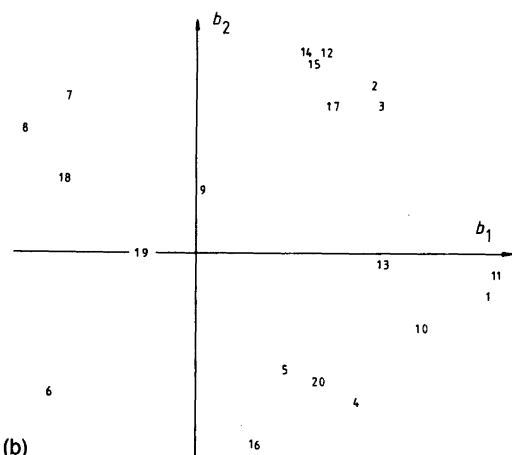
Table 2. Screening experiments with selected Lewis acids

Reaction ^a	Lewis acid	Maximum yield (%)	t_{50} (min)
A	AlCl ₃	39	1.9
	CoCl ₂	0	—
	MnCl ₂	0	—
	PCl ₃	0	—
	SiCl ₄	0	—
	SnCl ₄	38	22.1
	TiCl ₃	0	—
	TiCl ₄	45	3.1
	ZnCl ₂	44	378
B	AlCl ₃	50	0.1
	CoCl ₂	0	—
	MnCl ₂	0	—
	PCl ₃	0	—
	SiCl ₄	0	—
	SnCl ₄	2.5	20.2
	TiCl ₃	13	1.5
	TiCl ₄	26	7.0
C	AlCl ₃	94.1	0.8
	CoCl ₂	3.5	630
	MnCl ₂	6.6	71.2
	PCl ₃	0	—
	SiCl ₄	0	—
	SnCl ₄	0	—
	TiCl ₃	25.7	36.0
	TiCl ₄	55.0	750
ZnCl ₂	5.0	1800	

^aA: Alkylation of silyl enol ether, B: Diels-Alder reaction, C: Friedel-Crafts reaction. See Scheme 1.



(a)



(b)

didate chosen so that the remaining 2 better candidates and the new 1 form a new simplex (triangle) oriented away from the first poorest candidate. Determine the worst outcome with the new simplex, etc. This allows for a systematic iterative search for a suitable acid catalyst.

These strategies are flexible and can take any prior information into account, such as details of the reaction mechanism. They can also cope with optimization by allowing for a systematic search around the winning candidate in a screening experiment so that various criteria of optimality

Fig. 2. (a) PC projection in the augmented study. (b) Loadings in the augmented study.

such as yield, selectivity, ease of work-up, cost, etc. can be fulfilled.

Discussion

A selection strategy for screening experiments must enable chemically relevant test objects to be found. The strategies outlined above fulfill this criterion. The 3 reactions used to evaluate the initial study are all well established synthetic procedures. The 9 test candidates were selected based solely on their distribution in the PC projection, Fig. 1 (a). Boron trifluoride was an obvious candidate but was omitted due to the fact that it is a gas and difficult to dose. The results shown in Table 2 clearly demonstrate that the winning candidate in all 3 reactions is in complete agreement with established results: (A) titanium tetrachloride as the preferred catalyst in the *Reetz* alkylation of silyl enol ethers⁴; (B) aluminum trichloride as a suitable catalyst for *Diels-Alder* reactions¹⁵; (C) aluminum trichloride as a preferred catalyst in *Friedel-Crafts* acylation.¹⁶ Iron(III) chloride has been reported to be a better catalyst than aluminum trichloride in some acylations¹⁷ so it is interesting to find that is very close to aluminum trichloride in the projections.

The PC projections also seem to contain information on the hard/soft properties of acids.² In Fig. 1 (a) the t_1 axis seems to describe this property. The very hard acid BF_3 is found on the extreme right in the projection and the soft acids MoS_2 , CoCl_2 , and Me_3B very far to the left. With the more complete data set in Table 3 (a), a slightly more complicated picture emerges and in the corresponding PC projection, Fig. 2 (a), the hard/soft properties are described by both components in a direction going from the lower left to the upper right quadrants. A tentative hard/soft scale could thus be defined as coordinates along an axis from the very hard acid, silicon tetrafluoride (48) to the very soft acid, copper(I) iodide (97).

A problem which is encountered whenever a set of descriptors is compiled for a large number of objects is that the data matrix cannot be completely filled. There are always missing data. Initially, about 35 Lewis acid descriptors were considered. However, some of them were available only for a handful of acids. In Table 3, there are still data lacking for some of the acids. This does

not pose any serious problems in the data analytic method used, PC analysis by the SIMCA program package, since this method tolerates a few (<10 %) missing data in some variables without serious loss of the overall information.

Conclusions

Chemistry of today suffers from a "data explosion" – any single chemical system can be characterized by a large number of measured properties; any single experiment can produce a multitude of measured responses. It is impossible to cope with the situation by mere inspection of tabulated data or by simple bivariate correlation. The only reasonable way to handle this is to use computer-assisted multivariate methods. The methods outlined in this paper and in Ref. 3 are examples of a general computer-assisted strategy for selecting test objects in synthetic screening. The strategy also allows for a systematic optimization of reaction strategies by sequential simplex search.

Calculations and experimental

The calculations were carried out on a Zampo (8-bit) or a Toshiba T1500 (16-bit) microcomputer. PC modelling was accomplished by the SIMCA program package (SIMCA-3B version). The program is written in BASIC and versions for standard CP/M or IBM PC-compatible microcomputers are available from Sepanova AB, Östrandsvägen 14, S-122 43 Enskede, Sweden and from Principal Data Components, 2505 Shepherd Blvd., Columbia, MO 65201, USA.

Lewis acids used in the screening experiments were supplied by Aldrich or Sigma. *Pro analysi* quality was used. The acids were stored in a desiccator over Siccapent® (Merck) and all handling of the acids was carried out in an atmosphere of dry nitrogen.

GLC analyses were performed on a PYE UNICAM GCD with a flame ionization detector. HPLC analyses were achieved using a LDC high pressure liquid chromatograph equipped with a Constametric® III pump and a Spectromonitor® III detector. Peak areas were used for quantification by the internal standard technique; a Milton Roy C-10 integrator was used.

Table 3. Lewis acids and descriptors^a used in principal component analysis

Acids	Descriptors									
	1	2	3	4	5	6	7	8	9	10
1 TiCl ₂	23.6	513.8	464.4	87.4	69.83	2.25	1308.5	475	3.13	585.62
2 TiCl ₃	51.3	720.9	653.5	139.7	97.15	2.3	440	660	2.64	1220.45
3 TiCl ₄	94.5	804.2	737.2	252.34	145.18	2.19	-25	136.4	1.726	2220
4 VCl ₃	52.8	561	-	-	-	-	-	-	3	1296.51
5 VCl ₅	-	570.2	-	235.3	-	2.03	-28	148.5	1.816	2374.9
6 CrCl ₂	24	395.4	356.1	115.3	71.2	2.09	814	-	2.878	634.73
7 CrCl ₃	54.3	556.5	486.2	123	91.8	2.38	1152	1300	2.76	1356
8 MnCl ₂	24	481.29	440.5	118.24	72.93	2.09	650	1190	2.977	602.2
9 FeCl ₂	25.2	341.79	302.3	117.95	76.65	2.38	677	-	3.16	657
10 FeCl ₃	54.5	399.49	334	142.3	96.65	-	306	315	2.898	1365.4
11 CoCl ₂	25.5	312.5	269.9	109.2	78.5	2.53	7.24	1049	3.356	679.78
12 NiCl ₂	26.2	305.33	259.03	97.65	71.67	1.82	1001	973	3.55	700.619
13 CuCl	7.85	137.2	119.86	86.2	48.5	2.3407	429	1490	4.14	260.513
14 CuCl ₂	26.9	220.1	175.7	108.07	71.88	2.09	493	993	3.986	729.94
15 ZnCl ₂	26.8	415.05	369.398	111.46	71.34	2.05	283	732	2.91	665.1
16 BCl ₃	-	427.2	387.4	206.3	106.7	1.75	-107.3	12.5	1.349	1785
17 AlCl ₃	55.6	704.2	628.8	110.47	91.84	2.06	190	182.7	2.44	1310.51
18 GaCl ₃	57.4	523.4	455.2	135.2	-	2.09	77.9	201.3	2.47	1433
19 SiCl ₂	-	162.4	176.32	282	51.33	2	-	-	-	676.46
20 SiCl ₄	-	657	617	330.6	90.2	2.091	-70	57.57	1.483	2492.77
21 GeCl ₄	103.7	504.8	-	347.5	-	2.1	-49.5	84	1.8443	2488.6
22 SnCl ₂	22.7	350	302.1	122.5	-	2.42	246	652	3.94	581.93
23 SnCl ₄	-	511.3	440.1	258.6	165.3	2.31	-33	114.1	2.226	2227.7
24 PCl ₅	-	374.9	305	364.58	112.8	2.03	166.8	162	4.63	4159.3
25 AsCl ₃	55.9	305	259.4	216.3	-	2.161	-8.5	130.2	2.163	1386.5
26 SbCl ₃	49.4	382.2	323.7	184.7	108	2.325	73.4	283	3.14	1231
27 SbCl ₅	-	440.2	350.2	301.3	-	1.97	2.8	79	2.336	3537
28 AsCl ₅	-	-	-	-	-	-	-	-	-	3990
29 TiF ₂	26.1	682.34	694.9	255.56	58.86	1.88	-	-	-	585.62
30 TiF ₃	56	1436.2	1360.7	87.9	92.02	1.97	1200	1400	3.4	1220.45
31 TiF ₄	101.6	1649.3	1559.3	133.97	114.2	1.92	400	284	2.798	2220
32 VF ₃	57.6	-	-	-	-	-	800	-	3.363	1296.51
33 VF ₄	-	1404	-	121.4	-	-	325	-	2.975	2374.9
34 CrF ₂	21.1	779.9	711.3	89.7	-	1.72	894	1300	4.11	634.73
35 CrF ₃	58.1	1113.9	1046	93.95	-	1.9	1100	1200	3.8	1356
36 MnF ₂	25.7	795.5	-	92.26	66.78	1.724	856	-	3.98	602.2
37 FeF ₂	27.2	711.3	668.6	86.12	68.1	1.99	1000	-	4.09	657
38 FeF ₃	58.5	1046.4	840.9	98.4	-	1.92	1000	-	3.52	1365.4
39 CoF ₂	27.7	692.9	626.6	82.1	68.9	2.04	1200	1400	4.46	679.78
40 NiF ₂	28.5	651.4	604.1	73.6	64.06	1.72	1000	-	4.63	700.619
41 CuF	8.61	192.5	171.6	64.8	44.9	1.749	908	1100	-	260.513
42 CuF ₂	28.9	542.7	475.4	86.12	94.14	1.72	950	-	4.23	729.94
43 ZnF ₂	28.8	764.4	713.3	73.68	65.65	1.81	872	1500	4.95	665.1
44 BF ₃	-	1137	1120.33	254.12	50.46	1.295	-126.7	-99.9	2.99	1785
45 AlF ₃	61.2	1504.1	1425	66.44	75.1	1.63	1291	-	2.882	1310.51
46 GaF ₃	61.5	-	-	-	-	1.88	800	1000	4.47	1433
47 SiF ₂	-	587.85	598.27	256.18	44.5	1.591	-	-	-	676.46
48 SiF ₄	-	1614.9	1572.7	282.4	73.6	1.55	-90	-	-	2492.77
49 GeF ₄	108.7	1192.5	-	302.9	-	1.68	-32	-36.5	2.46	2488.6
50 SnF ₂	25	-	-	-	-	2.06	-	-	-	581.93
51 SnF ₄	-	-	-	-	-	1.86	705	-	4.78	2227.7
52 PF ₅	-	1595.8	1508.7	300.6	84.8	1.58	-83	-75	5.805	4152.3

Table 3. cont.

Acids	Descriptors									
	11	12	13	14	15	16	17	18	19	20
1 TiCl ₂	2431	120	-	-	-	-	-	570	-	1.54
2 TiCl ₃	5134	111	-	-	-	-	-	1110	-	-
3 TiCl ₄	9431	104	-	-	-	-	11.76	-54	0	-
4 VCl ₃	5322	101	-	-	-	-	15.8	3030	-	-
5 VCl ₅	-	91	-	-	-	-	11.77	113	-	-
6 CrCl ₂	2455	97	-	-	-	-	9.97	7230	-	1.66
7 CrCl ₃	5473	86	-	-	-	-	-	6890	-	-
8 MnCl ₂	2362	96	-	-	-	-	11.03	14350	-	1.55
9 FeCl ₂	2525	98	-	-	-	-	9.84	14750	-	1.83
10 FeCl ₃	5364	80	-	-	-	-	-	13450	-	-
11 CoCl ₂	2709	92	-	-	-	-	10	12.66	-	1.88
12 NiCl ₂	2753	90	-	-	-	-	11.23	6145	-	1.91
13 CuCl	921	88	34.6	45.2	.279	-.279	10.7	-40	-	1.9
14 CuCl ₂	2774	72	-	-	.484	-.242	12.89	1080	-	-
15 ZnCl ₂	2690	78	38.3	40.2	.328	-.16	12.9	-65	-	-
16 BCl ₃	-	106.1	58.5	45.8	.357	-.119	11.62	-59.9	0	2.04
17 AlCl ₃	5376	101.5	39.5	62.2	.576	-.192	12.01	-	1.97	1.61
18 GaCl ₃	5217	86.8	46	32.7	.312	-.104	11.96	-63	-	1.81
19 SiCl ₂	-	101	-	-	-	-	10.93	-	-	-
20 SiCl ₄	-	95.6	48.3	45.5	.44	-.11	11.8	-88.3	0	1.9
21 GeCl ₄	-	81.2	-	-	.264	-.066	11.68	-72	0	2.01
22 SnCl ₂	2276	93	-	-	-	-.16	7.3	-69	-	1.65
23 SnCl ₄	8355	75.3	41.4	31.6	.352	-.088	12.13	-115	0	1.96
24 PCl ₅	-	63	-	-	-	-.06	10.7	-67.8	0	-
25 AsCl ₃	-	73.8	48.2	18.7	.183	-.061	10.55	-79.9	1.55	2.18
26 SbCl ₃	5032	75	43.3	28.1	.294	-.098	10.2	-86.7	3.8	2.05
27 SbCl ₅	-	60.4	-	-	-	-	-	-120	-	-
28 AsCl ₅	-	-	-	-	-	-	-	-	-	-
29 TiF ₂	2724	-	-	-	-	-	-	-	-	1.54
30 TiF ₃	5644	144	-	-	-	-	-	1300	-	-
31 TiF ₄	10012	142	-	-	-	-	-	-	0	-
32 VF ₃	5895	134	-	-	-	-	-	2730	-	-
33 VF ₄	-	-	-	-	-	-	-	-	-	-
34 CrF ₂	2778	114	-	-	-	-	10.6	-	-	1.66
35 CrF ₃	5958	111	-	-	-	-	-	4370	-	-
36 MnF ₂	2644	111	-	-	-	-	11.38	10700	-	1.55
37 FeF ₂	2769	117	-	-	-	-	-	9500	-	1.83
38 FeF ₃	5870	110	-	-	-	-	-	13760	-	-
39 CoF ₂	2878	113	-	-	-	-	-	9490	-	1.88
40 NiF ₂	2845	112	-	-	-	-	-	2410	-	1.91
41 CuF	-	102	26.1	69.8	.366	-.366	-	-	-	1.9
42 CuF ₂	3046	91	-	-	-	-	-	1050	-	-
43 ZnF ₂	2930	99	27.2	63.3	.452	-.226	13.91	-38.2	-	-
44 BF ₃	-	154.3	71.5	86.7	.504	-.168	15.96	-	0	2.04
45 AlF ₃	5924	141	44.5	100.4	.729	-.243	-	-13.4	-	1.61
46 GaF ₃	6205	114	48.5	53.3	.456	-.152	-	-	-	1.81
47 SiF ₂	-	141	-	-	-	-.24	10.78	-	1.23	-
48 SiF ₄	-	142.6	58.7	80.8	.6	-.15	15.19	-	0	1.9
49 GeF ₄	-	112.5	59.8	51.2	.416	-.104	16.06	-50	0	2.01
50 SnF ₂	2551	116	-	-	-	-	-	-	-	1.65
51 SnF ₄	-	101	47.8	59.6	-	-	-	-	0	1.96
52 PF ₅	-	111.1	50.6	60.5	-	-	15.54	-	0	-

Table 3. cont.

Acids	Descriptors									
	1	2	3	4	5	6	7	8	9	10
53 AsF ₃	61.5	821.3	774.16	181.2	126.57	1.712	-8.5	-63	2.666	1386.5
54 SbF ₃	53.7	915.5	-	-	-	1.9	292	319	4.379	1231
55 SbF ₅	-	-	-	-	-	-	7	149.5	2.99	3537
56 AsF ₅	-	-	-	-	-	-	-80	-53	7.71	3990
57 TiBr ₂	22.9	402	383.2	119.7	77.82	2.4	500	935.8	4.31	585.62
58 TiBr ₃	50	548.5	523.8	176.6	101.71	2.4	-	794.2	-	1220.45
59 TiBr ₄	92.9	616.7	589.5	243.5	131.5	2.31	39	230	2.6	2220
60 VBr ₃	51.8	447.9	-	142.4	-	-	-	-	-	1297.51
61 VBr ₄	-	393.6	-	334.9	-	2.3	-	-	4	2379
62 CrBr ₂	23.3	338.9	-	-	-	2.24	844	-	4.356	634.73
63 CrBr ₃	53.1	426.8	-	-	-	2.57	1130	-	4.29	1356
64 MnBr ₂	23.2	384.9	-	138.1	-	2.24	-	-	4.385	602.2
65 FeBr ₂	24.4	249.8	238.1	140.6	80.2	2.24	684	-	4.636	657
66 FeBr ₃	53.7	268.2	-	173.7	-	-	-	-	-	1365.4
67 CoBr ₂	24.9	221	-	134	-	2.24	844	-	-	679.78
68 NiBr ₂	25.5	212.11	-	136	-	2.24	963	-	5.098	700.619
69 CuBr	7.78	104.6	100.8	96.11	54.73	2.173	492	1345	4.98	260.513
70 CuBr ₂	26.6	141.8	-	133.9	-	2.4597	498	-	4.77	729.94
71 ZnBr ₂	26.2	328.65	312.13	138.5	-	2.24	394	650	4.201	665.1
72 BBr ₃	-	239.7	238.5	229.7	128	1.87	-46	91.3	2.6431	1785
73 AlBr ₃	54.3	527.2	504.4	180.2	101.7	2.21	97.5	263.3	2.64	1310.51
74 GaBr ₃	56.5	386.9	-	180	-	2.28	121.5	278.8	3.69	1433
75 SiBr ₂	-	-	-	-	-	-	-	-	-	676.46
76 SiBr ₄	-	92.13	-	-	-	2.15	-	-	-	2492.2
77 GeBr ₄	101.7	330.8	-	396.9	-	2.31	26.1	186.5	3.132	2488.6
78 SnBr ₂	22.1	264.8	248.9	146	-	2.55	215.5	620	5.117	581.93
79 SnBr ₄	-	377.4	350.2	264.4	-	2.44	31	202	3.34	2227.7
80 PBr ₅	-	269.9	-	-	-	2.1	100	106	-	4159.3
81 AsBr ₃	54.7	130	159	363.87	76.16	2.33	32.8	221	3.54	1386.5
82 SbBr ₃	48.4	-	-	-	-	2.51	96.6	280	4.148	1231
83 SbBr ₅	-	-	-	-	-	-	-	-	-	3537
84 AsBr ₅	-	-	-	-	-	-	-	-	-	3990
85 TiI ₂	22	264	258.9	138.1	86.22	2.59	600	1000	4.99	585.62
86 TiI ₃	48.9	322.2	318.47	192.5	116.8	-	-	727	-	1220.45
87 TiI ₄	91.2	375.7	371.5	249.4	125.65	-	150	377.1	4.3	2220
88 VI ₃	50.7	280.5	-	203.1	-	-	-	-	-	1296.51
89 VI ₄	-	-	-	-	-	-	-	-	-	2374.9
90 CrI ₂	22.4	158.3	-	-	-	2.43	868	800	5.196	634.73
91 CrI ₃	51.9	205.1	-	199.6	-	-	600	350	4.915	1356
92 MnI ₂	22.5	331	-	-	-	2.43	638	500	5	602.2
93 FeI ₂	23.7	113	86.5	170	112.9	2.43	587	1093	5.315	657
94 FeI ₃	52.8	71	-	-	-	-	-	-	-	1365.4
95 CoI ₂	24.1	87.9	-	153.2	-	2.43	515	570	5.68	679.78
96 NiI ₂	24.9	78.2	-	154	-	2.43	797	-	5.834	700.619
97 CuI	7.65	67.8	69.5	96.7	54.06	2.6169	605	1290	5.62	260.513
98 CuI ₂	25.9	7.1	-	-	-	2.43	-	-	-	729.94
99 ZnI ₂	25.5	208.03	208.95	161.1	-	2.38	446	624	4.7363	665.1
100 BI ₃	-	71.13	20.72	349.18	70.79	2.1	-	-	-	1785
101 AlI ₃	52.9	313.8	300.8	159	98.7	2.53	191	360	3.98	1310.51
102 GaI ₃	55.4	239.4	-	203.9	-	2.44	212	345	4.15	1433
103 SiI ₂	-	144	-	-	-	-	-	-	-	676.46
104 SiI ₄	-	199	-	265.6	-	2.435	-	-	-	-

Table 3. cont.

Acids	Descriptors									
	11	12	13	14	15	16	17	18	19	20
53 AsF ₃	—	116.3	58.5	41.7	.321	-.107	12.3	—	2.59	2.18
54 SbF ₃	5295	106	50.8	51.2	.438	-.146	—	-46	—	2.05
55 SbF ₅	—	—	—	—	—	—	—	—	—	—
56 AsF ₅	—	—	—	—	—	—	—	—	0	—
57 TiBr ₂	2360	—	—	—	—	—	—	640	—	1.54
58 TiBr ₃	5012	95	—	—	—	—	—	660	—	—
59 TiBr ₄	9288	89	—	—	—	—	10.55	—	0	—
60 VBr ₃	5192	87	—	—	—	—	—	2896	—	—
61 VBr ₄	—	90	—	—	—	—	—	—	—	—
62 CrBr ₂	2377	80	—	—	—	—	—	—	—	1.66
63 CrBr ₃	5355	72	—	—	—	—	—	—	—	—
64 MnBr ₂	2304	81	—	—	—	—	—	—	—	1.55
65 FeBr ₂	2464	83	—	—	—	—	—	13600	—	1.83
66 FeBr ₃	5268	71	—	—	—	—	—	—	—	—
67 CoBr ₂	2648	79	—	—	—	—	—	13000	—	1.88
68 NiBr ₂	2699	76	—	—	—	—	—	5600	—	1.91
69 CuBr	879	80	33.6	36.5	.235	-.235	—	-49	—	1.9
70 CuBr ₂	2711	63	—	—	—	—	—	653.3	—	—
71 ZnBr ₂	2632	66	35.7	30.3	.266	-.133	—	—	—	—
72 BBr ₃	90	88	53.8	33.9	.285	-.095	—	—	—	2.04
73 AlBr ₃	5247	87	37.4	48.7	—	-.17	10.91	—	—	1.61
74 GaBr ₃	4966	72.1	43	23	.24	-.08	—	—	—	1.81
75 SiBr ₂	—	86	—	—	—	—	12	—	—	—
76 SiBr ₄	—	78.8	—	—	.36	-.09	14	-128.6	0	1.9
77 GeBr ₄	—	67.2	46.4	17.1	.188	-.047	10.9	—	0	2.01
78 SnBr ₂	2211	80.5	—	—	—	—	6.84	—	—	1.65
79 SnBr ₄	7970	63.6	38.5	25.2	.272	-.068	11.1	-149	0	1.96
80 PBr ₅	—	—	—	—	—	—	—	—	—	—
81 AsBr ₃	5497	61.2	45.2	10.8	.114	-.038	10.19	-106	1.7	2.18
82 SbBr ₃	4954	63.1	40.6	19.8	.225	-.075	9.77	-115	2.8	2.05
83 SbBr ₅	—	—	—	—	—	—	—	—	—	—
84 AsBr ₅	—	—	—	—	—	—	—	—	—	—
85 TiI ₂	2259	—	—	—	—	—	—	1790	—	1.54
86 TiI ₃	4845	80	—	—	—	—	—	160	—	—
87 TiI ₄	9108	73	—	—	—	—	9.27	—	0	—
88 VI ₃	5058	72	—	—	—	—	—	—	—	—
89 VI ₄	—	—	—	—	—	—	—	—	—	—
90 CrI ₂	2269	62	—	—	—	—	—	—	—	1.66
91 CrI ₃	5201	54	—	—	—	—	—	—	—	—
92 MnI ₂	2212	66	—	—	—	—	—	14400	—	1.55
93 FeI ₂	2382	68	—	—	—	—	—	13600	—	1.83
94 FeI ₃	5117	57	—	—	—	—	—	—	—	—
95 CoI ₂	2569	63	—	—	—	—	—	10760	—	1.88
96 NiI ₂	2607	62	—	—	—	—	—	3875	—	1.91
97 CuI	835	71	33	22.1	.153	-.153	—	-63	—	1.9
98 CuI ₂	2640	48	—	—	—	—	—	—	—	—
99 ZnI ₂	2549	51	35	16.3	.152	-.076	—	-98	—	—
100 BI ₃	—	64.7	50	17	.156	-.052	—	—	—	2.04
101 AlI ₃	5070	68	37	33.1	.369	-.123	9.66	—	—	1.61
102 GaI ₃	4611	58.9	41.2	9.7	.114	-.038	9.4	-149	—	1.81
103 SiI ₂	—	70	—	—	—	—	—	—	—	—
104 SiI ₄	—	59.5	—	—	.216	-.054	—	—	0	1.9

Table 3. cont.

Acids	Descriptors									
	1	2	3	4	5	6	7	8	9	10
105 GeI ₄	100.2	37.7	–	429.1	–	2.49	144	440	4.322	2488.6
106 SnI ₂	21.3	143.5	–	167.8	–	2.73	320	714	5.285	581.93
107 SnI ₄	–	143.9	143.9	168.6	84.9	2.67	144.2	364.5	4.473	2227.7
108 PI ₅	–	–	–	–	–	–	–	–	–	4159.3
109 AsI ₃	53.8	–	–	–	–	2.515	146	403	4.39	1386.5
110 Sbl ₃	47.3	–	–	–	–	2.67	170	401	4.917	1231
111 Sbl ₅	–	–	–	–	–	–	79	400.6	–	3537
112 AsI ₅	–	–	–	–	–	–	76	–	3.93	3990
113 PCl ₃	–	319.7	272.3	217.1	–	2.03	–112	75.5	1.5751	–
114 PBr ₃	–	184.5	175.7	240.2	–	2.18	–41.5	173.5	2.852	–
115 PI ₃	–	46.6	–	–	–	2.43	61.2	200	4.18	–
116 PF ₃	–	918.8	897.5	273.24	58.7	1.546	–151.5	–101.8	3.9	–

*Compiled from standard reference tables (Refs. 5, 6) and other sources (Refs. 7–13). Descriptors: 1, coordinate bond energy (eV); 2, negative of standard enthalpy of formation (kJ mol⁻¹); 3, negative of standard Gibbs energy of formation (kJ mol⁻¹); 4, standard entropy (J mol⁻¹ K⁻¹); 5, heat capacity (J mol⁻¹ K⁻¹); 6, mean bond length (Å); 7, melting point (°C); 8, boiling point (°C); 9, density (10³ kg m⁻³); 10, standard enthalpy of formation of Mⁿ⁺ species (kcal mol⁻¹);

Procedures for screening experiments

A: Reetz alkylation: A 20 ml dichloromethane solution containing 1.70 g (10 mmol) of trimethylsilyloxycyclohexane, 0.93 g (10 mmol) of *tert*-butyl chloride, and an accurately weighed amount of nitrobenzene (internal standard) was maintained at 0°C by magnetic stirring. To this was added, in one portion a cooled (0°C) solution of 10 mmol of the Lewis acid in 20 ml of dichloromethane. The reaction mixture was maintained at 0°C by means of an ice bath.

Analysis: Aliquots (0.5 ml) were withdrawn at regular intervals and diluted with 5 ml of dichloromethane. The sample was shaken with 10 ml of aqueous 8% NaHCO₃ until the organic layer became clear. This was analyzed by GLC using a 1.5 m × 4 mm (i.d.) glass column packed with 5% PEG + 0.5% KOH on Chromosorb® W-AW 100–120 mesh.

B: Diels-Adler reaction: A 20 ml dichloromethane solution containing 1.42 g (10 mmol) of dimethyl acetylenedicarboxylate and an accurately weighed amount of nitrobenzene (internal standard) was agitated magnetically while a solution

of 10 mmol of the Lewis acid in 20 ml of dichloromethane was added. The resulting mixture was stirred in a thermostated water bath at 22°C. The reaction was started by the rapid addition of 0.68 g (10 mmol) of furan in 10 ml of dichloromethane. The reaction mixture was stirred at 22°C and samples were withdrawn at regular intervals. Analysis: 5 drops of the reaction mixture were diluted with 5 ml of methanol and 0.5 ml of this solution was further diluted with 5 ml of a methanol/water mixture, 38/62 (v/v). This very dilute solution was subjected to isocratic HPLC analysis using the same methanol/water mixture as eluent and a Hypersil® C-18 column. Peaks were detected by UV absorption at 289 nm.

C: Friedel-Crafts acylation: A 20 ml dichloromethane solution containing 10 mmol of the Lewis acid was refluxed with magnetic stirring while 10 ml of the reactant solution was rapidly added. This solution contained 1.69 g (10 mmol) of 3-phenyl propanyl chloride and an accurately weighed amount of phenyl cyclohexane (internal standard). The mixture was maintained at reflux, samples (~0.5 ml) withdrawn at regular intervals

Table 3. cont.

Acids	Descriptors									
	11	12	13	14	15	16	17	18	19	20
05 GeI ₄	—	51.4	44.1	4.3	.052	-.013	9.42	-174	0	2.01
06 SnI ₂	2123	64	—	—	—	—	—	—	—	1.65
07 SnI ₄	—	50	37.3	12.5	.16	-.04	—	—	0	1.96
08 PI ₅	—	—	—	—	—	—	—	—	—	—
09 AsI ₃	4824	49	42.1	.9	.012	-.004	9	-142	.96	2.18
10 Sbl ₃	4867	48	38.5	7.8	.096	-.032	—	-147	1.58	2.05
11 Sbl ₅	—	—	—	—	—	—	—	—	—	—
12 AsI ₅	—	—	—	—	—	—	—	—	—	—
13 PCI ₃	—	78.5	—	—	—	—	9.91	-63.4	.79	2.19
14 PBr ₃	—	64.4	—	—	—	—	9.96	—	.61	2.19
15 PI ₃	—	44	—	—	—	—	9.15	—	0	2.19
16 PF ₃	—	118.7	—	—	—	—	11.5	—	—	2.19

1, lattice energy (exp. or calc.) (kJ mol⁻¹); 12, mean bond energy (kcal mol⁻¹); 13, covalent bond energy (kcal mol⁻¹); 14, ionic bond energy (kcal mol⁻¹); 15, partial charge on central atom (θ); 16, partial charge on ligand atom (ϵ); 17, ionization potential (gas phase) (eV); 18, magnetic susceptibility (measured at various temperatures (10⁻⁶ cgs)); 19, dipole moment (gas phase) (D); 20, atomic electronegativity of central atom in different oxidation states.

were shaken with 5 ml of acidulated water and analyzed by GLC. A 1.5 m × 4 mm i.d. glass column packed with 6% QF-1 on Chromosorb® W-AW, 100–120 mesh, was used.

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