Journal of Inclusion Phenomena and Molecular Recognition in Chemistry **23**: 203–212, 1995.

Computational Prediction of Trends in the Selectivity of Macrocyclic Receptors for Anions

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(Received 17 July 1995; in final form 28 September 1995)

Abstract. We seek a theoretical method which is capable of predicting trends in the binding affinity of macrocyclic receptors for various anions in aqueous solution. Success has been achieved in this endeavor by employing semiempirical methodology to compute the energetics of certain exchange reactions whereby anions are exchanged between a macrocyclic receptor and a cluster of water molecules. The method is computationally tractable with workstation-class computing hardware and is applicable to a wide range of guest/host systems. Computations for several anion/receptor systems are reported.

Key words. Anion-receptors, selectivity, semiempirical computations.

1. Introduction

Specificity in ion binding by macrocyclic hosts [1], termed 'molecular recognition technology', has led to the development of commercial cation separation systems [2]. It is likely that this technology can also be used for the recognition of specific anions and therefore the search for selective anion receptors is underway [3]. While the alkali metal cation selectivity of crown ethers was first reported in 1967 [4], and the first anion inclusion compounds were reported in 1968 [5], the development of cation molecular recognition agents has been far greater than that of corresponding anion receptors. Nevertheless, some selective anion receptors have been reported. An extensive list of citations has been given by Yang *et al.* [6]. Very recently, Kaufmann and Otten have reviewed the current state of the search for neutral selective anion receptors [7]. In order to aid in identifying new compounds which are likely candidates for anion binding, it is desirable to have available a computational method which is both efficient, and at a minimum, capable of reproducing the experimental trends in the selectivity of known anion binding agents [8]. This method can then be used as a screening tool for the selection of new synthetic goals. It is the main purpose of this paper to identify one such method. In Section 2 we discuss the considerations involved in selecting a theoretical model. Section 3 identifies several specific anion binding systems suitable for testing the

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model. The balance of the paper reports the results of calculations on these systems using the chosen method and discusses their implications.

2. Selection of Theoretical Technique

There exist three broad categories of theoretical methods for investigating molecular properties. In order of increasing complexity they are, the classical molecular mechanics (MM) methods, semiempirical methods, and *ab initio* methods. While techniques from all three of these categories have been applied to the study of cation binding, there have been very few theoretical treatments of anion binding systems [8–12]. This fact makes the selection of a theoretical technique difficult because the validity of the various available theoretical methods for the investigation of anion binding has not been well established. Moreover, screening potential compounds for optimum binding involves computing information about the intermolecular interactions, a notoriously difficult computational task.

Shirts and Stolworthy have shown convincingly that existing MM methods which approximate the molecular charge distribution with a finite set of point charges at the atomic centers (partial atomic charges) are poorly suited to the study of macrocycles which contain highly polar heavy atoms where the Coulomb interaction is dominant [13]. This inadequacy is largely due to the fixed partial atomic charge approximation which neglects important induction and polarization effects on the charge distribution. The development of fast and accurate empirical algorithms for approximating partial atomic charges to overcome this deficiency is underway [14–18] but a thoroughly tested and robust implementation remains a future achievement. In spite of these limitations, there have been some notable successes with MM methods for ion binding by polycyclic ethers and related macrocycles. In one landmark study, Wipff *et al.* applied MM methods to alkali metal cation binding by crown ethers [19]. Although their work did not recover the experimental trends in binding affinity, Wipff *et al.* made important contributions to the understanding of these prototype cation binding systems. A very recent and much more advanced treatment of the same systems has been reported by Thompson *et al.* who used a hybrid quantum-mechanical/molecular-mechanical (QM/MM) method [20]. Molecular mechanics methods have also been used with some success for these alkali metal ion/crown ether systems by Hay and coworkers [21, 22] and Hancock [23] who have described the metal-host interaction as a bonding one. Hay and coworkers [21, 22] developed their MM bonding parameters from minimal basis set *ab initio* calculations.

The application of MM methods to anion binding has focused almost exclusively on the receptor SC24 [24]. Wipff and Wurtz [11] have examined the nature of the binding sites on the receptor and the role of rigidity in its selectivity. Owenson and coworkers [9, 10] have investigated the structure of the receptor and the dynamics of Cl^- capture by SC24, reporting an interesting stepwise dehydration of the ion as it moves from the solvent into the cavity of the receptor. Lybrand *et al.* [8] have

reported good success in reproducing the halide anion selectivity of tetraprotonated SC24 using a thermodynamic cycle-perturbation method which, strictly speaking, is not a MM method but does employ empirical potentials. A disadvantage of their method is that the simulation must include a very large number of solvent molecules in addition to the anion and the receptor.

In principle, *ab initio* methods can provide any desired accuracy, given sufficient time and computational resources. A few calculations of atomic cation binding by macrocyclic hosts using *ab initio* methods have been reported [25, 26], the most advanced being a heroic effort by Glendening *et al.* [26], who studied the alkali metal cation selectivity of 18-crown-6. They reported that geometry optimization of one of the macrocycle/guest-cation complexes required more than a month of CPU time on a fast workstation and that other larger calculations required many hours on a CRAY C90. In spite of this extensive use of computational resources, agreement with experimental work [27] was reported to be qualitative or semiquantitative at best. Given that the 18-crown-6 system considered by Glendening *et al.* contains 18 heavy atoms and 42 atoms in total (43 when the guest ion is included), it is probably not currently practical to employ similar methods on the systems of interest here because they are all significantly larger and we intend to eventually screen many potential anion receptors.

Having ruled out the simple MM methods and the sophisticated *ab initio* methods, it is reasonable to pursue the third course of action, which is the use of semiempirical methods. Semiempirical methods have several advantages. First of all, computations with semiempirical methods on systems of the size of those considered here, while somewhat time consuming, are rapid enough to be practical. Secondly, semiempirical methods, unlike the classical MM methods, allow the redistribution of the molecular charge with changes in conformation. Finally, the semiempirical methods are based on an inherently quantum-mechanical description of the system and therefore include quantum-mechanical effects not incorporated into the MM methods. In the only previous theoretical treatment of anion binding by macrocyclic hosts to employ semiempirical methodology, the AM1 [28] semiempirical method was used. Yambe *et al.* [29] used more primitive semiempirical methods to study the complexation of Na^+ and K^+ by gas-phase crown ethers and made several important contributions to understanding the complexation in these systems. These results were subsequently reinforced with the more sophisticated *ab initio* methods [30].

Having settled on semiempirical methodology, it was then necessary to identify a specific semiempirical method for the problem at hand. While the AM1 method [28] is generally accepted to be the most accurate of the semiempirical techniques for many applications [31], it has two important limitations which exclude its use here. First, only a small fraction of the elements in the periodic table have been parameterized for AM1 calculations. Since we wish to eventually consider a wide range of guest/host systems, a method which is more broadly applicable is desired. Secondly, the AM1 semiempirical molecular model does not include *d* orbitals

or *d* electrons, the effects of which are known to be important in many cases of guest/host interactions. In light of these limitations the semiempirical ZINDO method with INDO1 parameters [32] was selected for this investigation. Fully 40% of the periodic table is parameterized for INDO1 calculations and where important, parameters for *d* orbitals are included. Finally, within the constraints of the available computational hardware and software, the INDO1 method is the least restrictive with respect to molecular size. The ultimate test of the choice of method, however, lies in its ability to reproduce experimental results. Herein, we aim to demonstrate that the chosen method withstands such a test.

3. Choice of Molecular Systems

Molecules must be chosen subject to certain constraints: (1) The molecular size must not exceed the limits of the available hardware and software; and (2) the software must contain INDO1 parameters for all elements represented in the molecule. In practice, even though INDO1 contains one of the most extensive parameter sets of any of the semiempirical methods, the second constraint is more restrictive, eliminating from consideration the interesting new mecuracarborand anti-crown anion receptors reported by Zhang *et al.*, for example [33]. Since we wish to establish the validity of the computational method for treating anion complexation, it is critical that experimental results for the binding affinity of these molecules for various anions be available for purposes of comparison. These considerations led to the selection of five compounds for this study: (A) compound (**2**) of Worm *et al.* [34]; (B) compound (**13**) of Schmidtchen [35]; (C) compound (**1**) of Graf and Lehn [36], (D) compound (**12**) of Schmidtchen [35]; and (E) compound (**L**) of Reilly *et al.* [37]. These systems are shown in parts A, B, C, D, and E of Figure 1, respectively. Compounds B, C, and D are macrotricyclic quaternary ammonium cations with C being the frequently studied tetraprotonated SC24. Compound A is an uncharged macrotricyclic borane–amine adduct, and compound E is a hexaprotonated octaazacryptand. This selection includes both neutral and charged species. In addition, it contains two systems with multiple ether linkages (C and D). Polyether systems are very difficult to treat with MM methods that employ fixed partial atomic charges [13] and represent a good test of any theoretical method. This selection also exhibits a broad range of selectivities. Compounds A, B and D exhibit greatest binding affinity for Br^-, compound C favors Cl^-, and compound E favors F^-.

4. Computations and Results

As done by Glendening *et al.* [26] and Wipff *et al.* [19], we have computed the energetics of certain ion exchange reactions to determine the selectivity of the

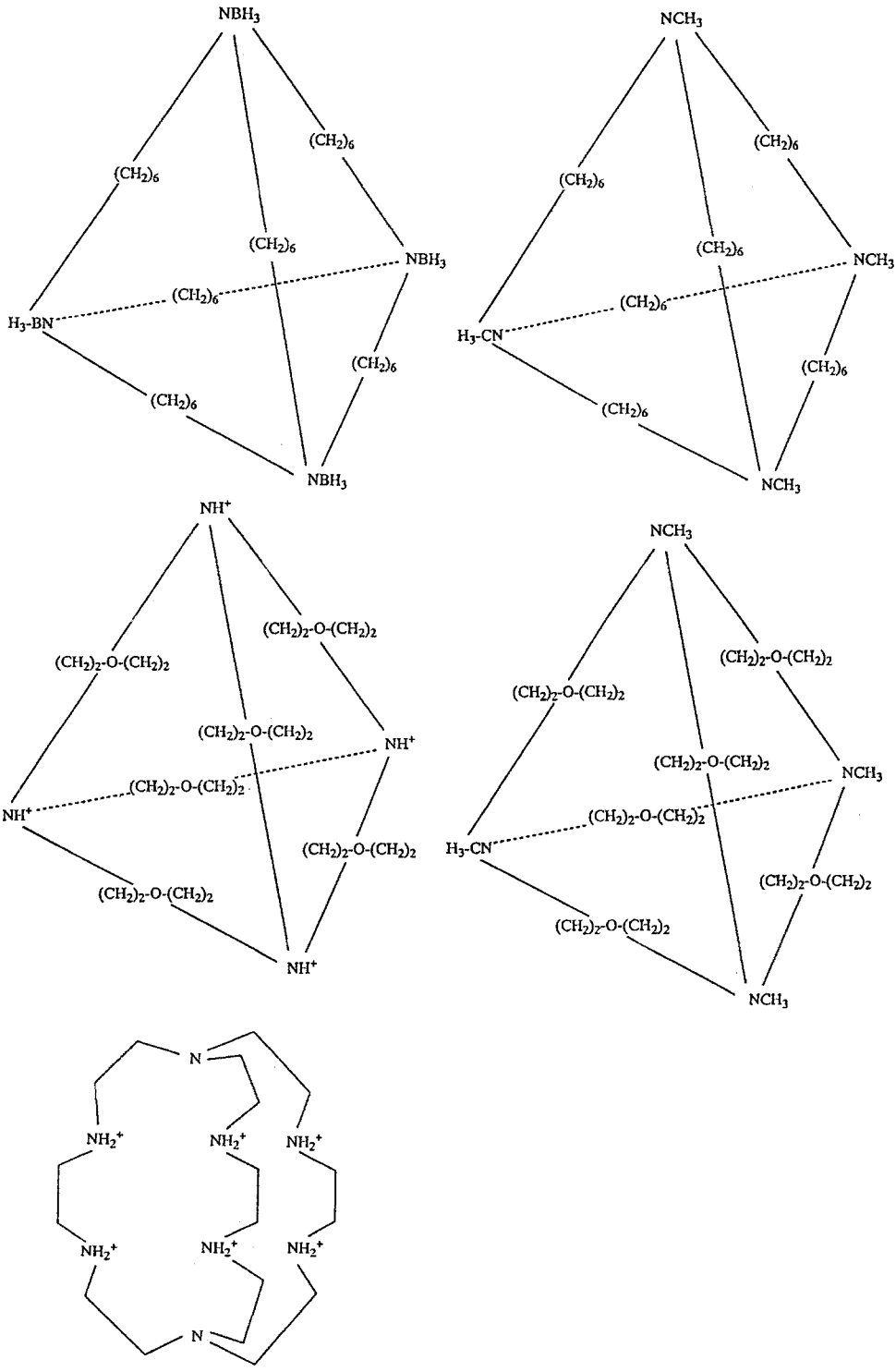


Figure 1. Receptor molecules used in this work. The overall molecular charges are: A = 0, B = 4, C = 4, D = 4, E = 6.

receptors for various ions in aqueous solution. The general reaction considered here is,

$$Br^-/\text{receptor} + X^-(H_2O)_n \rightarrow X^-/\text{receptor} + Br^-(H_2O)_n. \quad (1)$$

If reaction (1) is exothermic, it indicates favorable displacement of the bromide ion by the X^- anion in aqueous solution. Conversely, if the reaction is endothermic, the receptor binds the bromide ion more strongly than the X^- anion. Glendening *et al.* [26] used this ion exchange reaction method in conjunction with *ab initio* calculations to investigate the selectivity of 18-crown-6 for the various alkali metal cations. They have shown that the qualitative trends in the energetics are dependent on the number of water molecules of hydration n, but that in most cases just two water molecules ($n = 2$) are sufficient to recover the experimental trends in the selectivity of the receptor for various ions. We have considered clusters with $n = 2$, 3, and 4 waters of hydration. There are multiple stable structures at all levels of hydration. For the smaller clusters ($n = 2$, 3) the lowest energy structure has all of the water molecules directly coordinating the anion. For $n > 3$, the most stable structure has one or more of the water molecules in a hydrogen bonding position, effectively in the second hydration shell. These results are very similar to those reported by Glendening *et al.* for alkali metal cation water clusters [38]. Calculations were attempted for $n = 5$ but difficulties were encountered in obtaining reproducible results owing to the extremely 'loose' nature of these larger hydrated clusters.

As outlined previously, all computations were done with the INDO1 semiempirical method. The procedure used was as follows: First the receptor was drawn with a graphical-user-interface molecular editor [39] and optimized with molecular mechanics methods using the MM2 parameter set. Following this, conformational searching was done by MM optimization of each of 121 starting geometries selected by choosing all possible combinations of eleven separate values for each of two interatomic distances (atom distance search coordinates). The two interatomic distances were chosen to be approximately orthogonal. Each such search coordinate was selected so as to span the cavity of the receptor. Typically, one search coordinate ran from the center of one bridge to the center of an approximately opposing bridge, and the other connected a vertex with the center of an opposing bridge. The lowest energy conformation found in this search was then used as the starting point for the complexation calculations. An anion was then placed in the center of the cavity of the receptor and the structure optimized with the INDO1 semiempirical method. Several distortions of the optimized receptor/anion complex (typically 5–10) were then reoptimized to check the stability of the computed minima. For the anion/water clusters, automated conformational searching proved to be inefficient because these clusters are poorly treated by molecular mechanics methods. Instead, several visually reasonable starting structures were generated with the graphical-user-interface molecular editor and optimized with the INDO1

semiempirical method, resulting in total energies for several local (presumably low-lying) minima.

As noted by Wipff and Wurtz [11], in searching conformational space of a molecule of the size of the anion/receptor complexes considered here, it is virtually impossible to guarantee that the global minimum-energy conformer has been located. As we will demonstrate, however, the qualitative trends in binding affinities are typically quite insensitive to the exact molecular conformations considered. Table I shows the results of our ion exchange reaction calculations. The reaction considered is (1). The host/guest complex formed in the reaction is indicated in the first column of the table. For example, the notation 'A/F' indicates that the receptor considered in the reaction is 'A' and the 'X' species is F^-. The energy of the reaction was computed with,

$$\Delta E = (E_{\text{products}}) - (E_{\text{reactants}}), \tag{2}$$

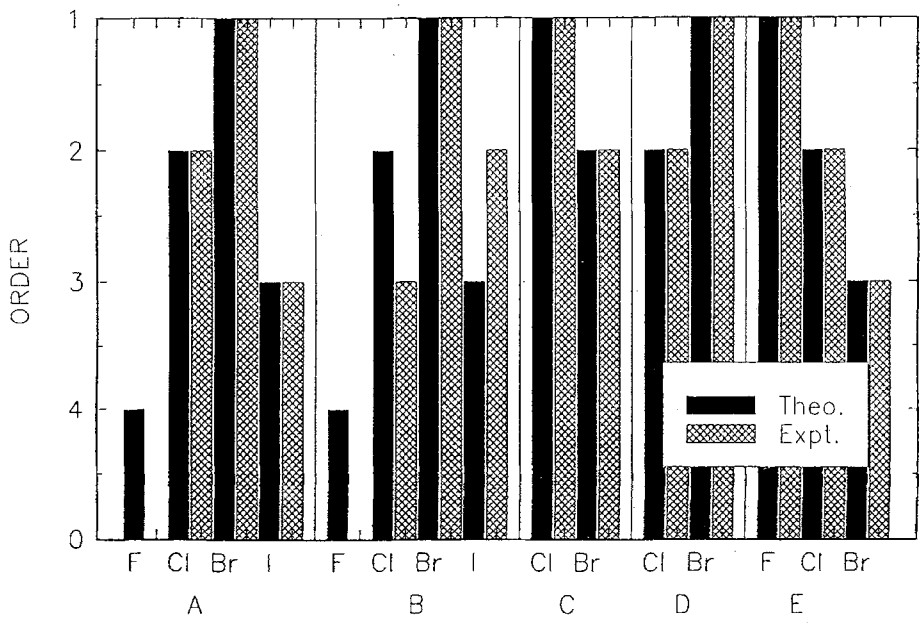
where E_{products} is the sum of the total energies of the product molecules as computed with the INDO1 method and $E_{\text{reactants}}$ is the sum of the total energies of the reactant molecules. The top row of the table indicates the number of waters of hydration included in the calculation. The energy of the reaction was computed in two different ways at each level of hydration, these are denoted 'L' and 'B' in the second row of Table I. Columns marked L give the energy of the reaction as computed by taking the total energy of each species present in the reaction to be that of the lowest energy conformer found for that species. Columns marked B give the energy of the reaction as computed by taking the total energy for each species present in the reaction to be a Boltzmann average of the energies of all conformers found for that species. (The temperature was taken to be 300 K.) The experimental ordering from the literature, where available, is given in the column marked 'expt'.

It is evident from Table I that the trends in binding affinity predicted by these exchange reaction calculations are independent of the method used (L or B) in virtually all cases, suggesting that the results are not critically dependent upon locating the best possible conformation for each reactant and product. It appears to be sufficient to locate a reasonable sample of energetically low-lying conformations for each species. Note that typically the computed results are also qualitatively the same for all levels of hydration considered. Only in the case of compound D is the order of selectivity dependent on the level of hydration, and in that case the experimentally observed ordering is recovered at the highest level of hydration, as should be expected. For the other compounds, the computed ordering is the same at all levels of hydration. Most importantly, in all cases, the calculations at the $(H_2O)_4$ level of hydration correctly predict which halide ion is most highly favored by the receptor, although typically lower levels of hydration are sufficient. It is not surprising that the calculations on receptor D are more sensitive to the level of hydration considered since this compound exhibits only a slight preference for Br^- over Cl^- [35]. It appears that reproducing such a subtle preference requires the more detailed calculation.

Table I. Energies for reaction (1) in kcal/mol. The top row of the table indicates the number of waters of hydration included in the calculation. The energy of the reaction was computed in two different ways at each level of hydration, these are denoted 'L' and 'B' in the second row of the table. Columns marked L give the energy of the reaction as computed by taking the total energy of each species present in the reaction to be that of the lowest energy conformer found for that species. Columns marked B give the energy of the reaction as computed by taking the total energy for each species present in the reaction to be a Boltzmann average of the energies of all conformers found for that species. (The temperature was taken to be 300 K.) The experimental ordering from the literature, where available, is given in the column marked 'expt'. Citations for the experimental results are: A [34], B [35], C [36], D [35], E [37].

(H_2O)	2		3		4		
	L	B	L	B	L	B*	expt.
A/F	50.8	50.6	42.2	42.2	73.7	73.7	–
A/Cl	0	0	0.6	0.6	6.9	6.9	2
A/Br	0	0	0	0	0	0	1
A/I	7.5	7.4	5.6	5.6	12.6	12.6	3
B/F	42.0	41.8	33.4	33.4	64.9	64.9	–
B/Cl	1.9	1.9	2.5	2.5	8.8	8.8	3
B/Br	0	0	0	0	0	0	1
B/I	7.5	7.4	5.6	5.6	12.6	12.6	2
C/Cl	−15.7	−15.7	−15.1	−15.1	−8.8	−8.8	1
C/Br	0	0	0	0	0	0	2
D/Cl	−6.3	-6.3	-5.6	-5.6	0.6	0.6	2
D/Br	0	0	0	0	0	0	1
E/F	−55.2	−55.6	−63.8	−64.0	−32.3	−32.5	1
E/Cl	−10.0	−10.2	−9.4	−9.6	−3.1	−3.3	2
E/Br	0	0	0	0	0	0	3

The qualitative trends in the binding affinities are summarized in Figure 2. The experimentally and theoretically determined ordering of binding affinity of each of the five compounds for various halide ions is shown. The solid bars indicate the theoretically determined ordering and the shaded bars indicate the ordering taken from experimental results reported in the literature. Smaller numbers denote more strongly bound species so that an ordinal of 1 (the highest bar) corresponds to the most strongly bound complex. When no bar is present it indicates that data is not available. The theoretical results are from calculations involving four waters of hydration, the most elaborate calculations undertaken here. Note that in all cases the calculations correctly predict which anion is most strongly complexed by the receptor. In addition, the ordering of the less strongly bound anions is also properly reproduced for all receptors except B. We are unsure of the source of this error. Given the remarkable structural similarity of A and B, however, it is notable that the ordering is not the same for these two compounds.



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It is important to note that the calculations reported here show the selectivity of a given receptor for various anions all of which have the same charge. It remains to be determined whether or not this method can be used in conjunction with anions of different charges. In addition, there is the related but subtly different problem of computing the selectivity of various receptors for a given anion, which must be addressed in order to compare the merits of the different receptors as binding agents for a specific anion. Both of these issues deserve future consideration.

5. Conclusions

We have computed trends in the binding affinity of several anion receptors for the halide ions and shown that when used to compute the energetics of certain ion exchange reactions, the INDO1 semiempirical method predicts selectivities in agreement with experimental results from the literature. In addition, we have shown that typically, the computed results are not highly dependent upon locating the best possible conformation for each reactant and product. This observation is quite important for systems the size of typical anion receptors because it is very difficult to be certain that one has located the global-minimum energy conformation. Our

success suggests that this method may be useful as a screening tool for the selection of new synthetic goals in the development of new abiotic anion receptors.

References

1. R.M. Izatt, J.S. Bradshaw, S.A. Nielsen, J.D. Lamb, J.J. Christensen, and D. Sen: *Chem. Rev.* **85**, 271 (1985).
2. J.S. Bradshaw, R.M. Izatt, R.L. Bruening, and J.J. Christensen: *U.S. Patent* 4,943,375 (Jul. 24, 1990).
3. R.M. Izatt, K. Pawlak, J.S. Bradshaw, and R.L. Bruening: *Chem. Rev.* **91**, 1721 (1991).
4. C.J. Pedersen: *J. Am. Chem. Soc.* **89**, 7017 (1967).
5. C.H. Park and H.E. Simmons: *J. Am. Chem. Soc.* **90**, 2431 (1968).
6. X. Yang, C.B. Knobler, Z. Zheng, and M.F. Hawthorne: *J. Am. Chem. Soc.* **116**, 7142 (1994).
7. D.E. Kaufmann and A. Otten: *Angew. Chem. Int. Ed. Engl.* **33**, 1832 (1994).
8. T.P. Lybrand, J.A. McCammon, and G. Wipff: *Proc. Natl. Acad. Sci. U.S.A.* **83**, 833 (1986).
9. B. Owenson, R.D. Macelroy, and A. Pohorille: *J. Mol. Struct. THEOCHEM* **179**, 467 (1988).
10. B. Owenson, R.D. Macelroy, and A. Pohorille: *J. Am. Chem. Soc.* **110**, 6992 (1988).
11. G. Wipff and J.-M. Wurtz: *New J. Chem.* **13**, 807 (1989).
12. S. Jacobson and R. Pizer: *J. Am. Chem. Soc.* **115**, 11216 (1993).
13. R.B. Shirts and L.D. Stolworthy: *J. Incl. Phenom.* **20**, 297 (1995).
14. A.K. Rappe and W.A. Goddard: *J. Phys. Chem.* **95**, 3358 (1991).
15. Z. Su: *J. Comput. Chem.* **14**, 1036 (1993).
16. L. von Szentpály and I.L. Shamovsky: *J. Molec. Struct. THEOCHEM* **305**, 249 (1994).
17. U. Sternberg, F.T. Koch, and M. Möllhoff: *J. Comput. Chem.* **15**, 524 (1994).
18. D.B. Kireev, V.I. Fetisov, and N.S. Zefirov: *J. Mol. Struct. THEOCHEM* **304**, 143 (1994).
19. G. Wipff, P. Weiner, and P. Kollman: *J. Am. Chem. Soc.* **104**, 3249 (1982).
20. M.A. Thompson, E.D. Glendening, and D. Feller: *J. Phys. Chem.* **98**, 10465 (1994).
21. B.P. Hay, J.R. Rustad, and C.J. Hostetler: *J. Am. Chem. Soc.* **115**, 11158 (1993).
22. B.P. Hay and J.R. Rustad: *J. Am. Chem. Soc.* **116**, 6316 (1994).
23. R.D. Hancock: *Acc. Chem. Res.* **23**, 253 (1990).
24. E. Graf and J-M. Lehn: *J. Am. Chem. Soc.* **98**, 6403 (1976).
25. A. Pullman, C. Giessner-Prettre, and Y.V. Kruglyak: *Chem. Phys. Lett.* **35**, 156 (1975).
26. E.D. Glendening, D. Feller, and M.A. Thompson: *J. Am. Chem. Soc.* **116**, 10657 (1994).
27. A.R. Katritzky, N. Malhotra, R. Ramanathan, R.C. Kemerait, Jr., J.A. Zirmnerman, and J.R. Eyler: *Rapid Commun. Mass Spectrosc.* **6**, 25 (1992).
28. M.J.S. Dewar, E.G. Zoebisch, E.F. Healy, and J.J.P. Stewart: *J. Am. Chem. Soc.* **107**, 3902 (1985).
29. T. Yamabe, K. Hori, K. Akagi, and K. Fukui: *Tetrahedron* **35**, 1065 (1979)
30. K. Hori, H. Yamada, and T. Yamabe: *Tetrahedron* **39**, 67 (1983).
31. I.N. Levine: *Quantum Chemistry*, Prentice Hall, Englewood Cliffs, NJ, Ch. 17 (1991).
32. ZINDO, J. Ridley and M. Zerner: *Theoret. Chim. Acta* **32**, 111 (1973). J. Ridley and M. Zerner: *Theoret. Chim. Acta* **42**, 223 (1976), as implemented in the CAChe Worksystem, CAChe Scientific, Inc. Beaverton, OR, U.S.A.
33. Z. Zheng, C.B. Knobler, C.E. Curtis, and M.F. Hawthorne: *Inorg. Chem.* **34**, 432 (1995).
34. K. Worm, F.P. Schmidtchen, A. Schier, A. Schäfer, and M. Hesse: *Angew. Chem. Int. Ed. Engl.* **33**, 327 (1994).
35. F.P. Schmidtchen: *Angew. Chem. Int. Ed. Engl.* **16**, 720 (1977).
36. E. Graf and J-M. Lehn: *J. Am. Chem. Soc.* **97**, 5022 (1975).
37. S.D. Reilly, G.R.K. Khalsa, D.K. Ford, J.R. Brainard, B.P. Hay, and P.H. Smith: *Inorg. Chem.* **34**, 569 (1995).
38. E.D. Glendening and D. Feller: *J. Phys. Chem.* **99**, 3060 (1995).
39. Editor V3.6, a part of the functionality of the CAChe Worksystem, CAChe Scientific, Inc. Beaverton, OR. U.S.A.