Letters

The close equivalence to earlier reported methods of a recently reported method of calculating hole sizes in macrocyclic ligands

The stability of complexes of macrocycles appears[1] to be governed by the match of the radius of the metal ion to the 'hole size' of the macrocyclic ligand. Hole sizes have previously been calculated using molecular mechanics (MM) calculations.[2–7] In a recent paper Drew *et al.*[8] report a MM method of calculating hole sizes which they clearly believe to be different from and superior to the previous methods. In brief, the steric strain in the M–L (metal–ligand) bond is given by expression (1)

$$U_{\text{M-L}} = \tfrac{1}{2}K(r - r^0)^2 \qquad (1)$$

in MM calculations,[9] where K is the force constant for bond length deformation of the M–L bond. The parameters r and r^0 are the observed and ideal or strain-free M–L bond lengths respectively in the complex. The best fit for the metal into the hole in the macrocycle, or any other ligand, must be when $U_{\text{M-L}} = 0$. In the method of Busch and co-workers[2,3] the best-fit size was found by putting $K = 0$, when the hole size was dictated by the ligand. In our calculations[4–7] r^0 was varied, and a curve of total strain energy for the complex, ΣU *vs.* r^0 (and also r) was plotted. This is seen in Figure 1 for $[\text{M(cyclam)(H}_2\text{O)}_2]^{n+}$ complexes (cyclam = 1,4,8,11-tetra-azacyclotetradecane), where the minimum (A) in the curve is the best-fit size. Calculations at all r^0 values used $K = 0.68$ mdyn Å^{-1} (dyn = 10^{-5} N), which is the value for the M–N bond in complexes of high-spin Ni$^{\text{II}}$ (taken as an average representative metal ion).[4,7] Drew *et al.*[8] have carried out identical calculations, which differ from ours only in that a constant value of $K = 25.0$ mdyn Å^{-1} was used to calculate the curves of ΣU *vs.* r^0. It was claimed[8] that this overcame problems associated with calculating hole sizes, arising from the possibility of some uncertainty in the value of K.

One can show quite simply that *the same hole size will be calculated for a given macrocycle quite independently of the value of K used.* In equation (1) the best-fit size with respect to bond length deformation comes when $U_{\text{M-L}} = 0$, *i.e.* the fit of the metal ion into the ligand regarding bond length is exact. $U_{\text{M-L}} = 0$ when either $K = 0$, which is the Busch method of determining hole sizes,[2,3] or when $r = r^0$. In the latter case the value of K used is immaterial, and the same hole size will be calculated whether a value of K of 0.68 mdyn Å^{-1} [4,7] or 25 mdyn Å^{-1} [8] is used. To demonstrate this, in Figure 1 I have plotted, for the cyclam complexes, ΣU *vs.* r^0 calculated using $K = 0.68$ and 25.0 mdyn Å^{-1}; all other parameters for the MM calculation were as used previously.[4–7] As expected, exactly the same hole size is calculated using the two widely differing values of K.

We first calculated a U *vs.* r curve for complexes because this gave more information than did the single-point calculation of Busch.[2,3] The minimum in such a curve (Figure 1, point A) is fixed with respect to both axes irrespective of the value of K used. However, the sharpness of the curve, which gives some idea of the relative sharpness of size selectivity of different ligands, is affected by K. Even so, a drastic increase in K has the effect only of stretching all the curves along the y axis, and if this is taken into account, the same conclusions will be reached about the relative sharpness of the size selectivity of different ligands. Increasing K to an unrealistically high value might lead one to draw incorrect conclusions if different conformers of the same ligand are compared. Thus, in a recent paper[6] we were able to show, in accord with experience, that one conformer of a macrocyclic complex was at a lower value of ΣU than a second, even at the best-fit size of the latter. However, using $K = 25.0$ mdyn Å^{-1}, which is a far higher force constant than for any known M–L bond, could sharpen up both ΣU *vs.* r^0 curves to the point where one would conclude that the second, less stable conformer would be the most stable near its best-fit size.

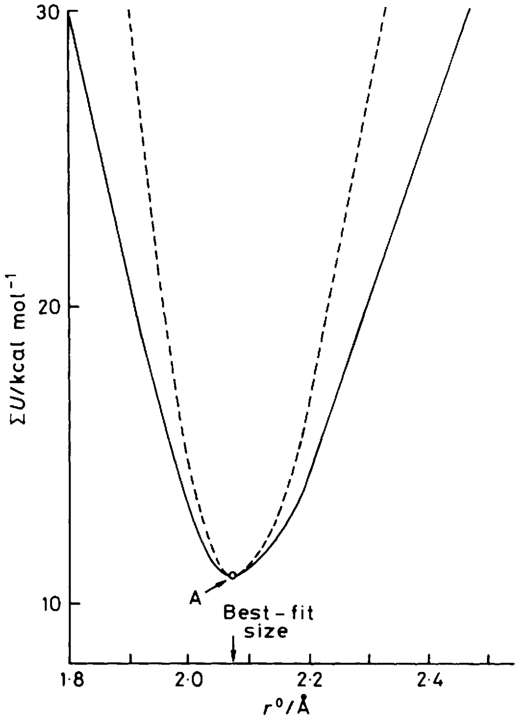

Figure 1. Variation of the total strain energy, ΣU (cal = 4.184 J), of the complexes $[\text{M(cyclam)(H}_2\text{O)}_2]^{n+}$ as a function of the ideal M–N bond length, r^0, of the metal ion M^{n+}, calculated with $K = 0.68$ (——) and 25.0 mdyn Å^{-1} (– – –). Note that point A (total strain energy of the complex at its best-fit size) is unaffected by the variation in K

I believe that had Drew *et al.*[8] examined my method[4–7] more closely, they would have realised its equivalence to their proposed method. Not only would they have seen that to call my method 'flawed' was unjustified, but that their proposed method offered no advantages, and indeed had some relative disadvantages. My method, of course, involves drawing the ΣU curve as a function of both r^0 and r, which allows one to determine how much the M–L bond will be deformed in accommodating the ligand. A possible improvement here would not be to use a constant value of K, but to allow it to vary inversely with r^0, since there appears[10] to be an inverse relationship between K and r within the first row of transition metal ions. However, experimentation with this shows[6] that the predicted bond lengths are not greatly affected by variation of K from 0.68 up to 2.25 mdyn Å^{-1}, the latter being the value of K appropriate to Co$^{\text{III}}$, the highest in this group of metal ion amine complexes, so that the small gain in precision may not be worth the extra complication.

Drew and Yates have subsequently shown (see below) that if the other force constants used are made dependent on the value of K, then small shifts in the position of the minimum (A) in the curve of ΣU *vs.* M–L bond length will be found. I do not believe that such shifts of 0.02 Å are of any significance. However, if there is a dependence of the position of A on the force constant, *then these authors have demonstrated that their calculations do not apply to real complexes.* The hole size calculated with a value of k_s = 25.0 mdyn Å^{-1} can only be appropriate for a metal ion with such a M–L force constant. No such metal ion exists, and indeed this is a higher force constant than for any known chemical bond.

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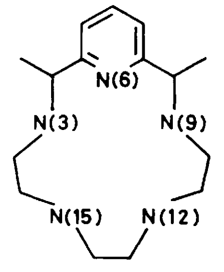
Drew and Yates reply. We do not accept Hancock's main criticism of our work [8,11] which is that the same hole size will be calculated for a given macrocycle quite independently of the value of the force constant k_s used in equation (2) [*cf.* equation (1)].

$$V_r = 0.5\, k_s(r - r_0)^2 \qquad (2)$$

Molecular mechanics calculations involve the summation of bond energy terms, bond angle terms, torsion angle terms, non-bonded repulsion terms, and in some force fields (including MM2,[12] the program we use) other terms such as dipole interactions and also cross terms. Hancock's statement is only true if all these other terms are totally independent of r_0. It has been the experience of those working on force fields for organic molecules that parameters in the force field are interdependent and have to be optimised together.[13–15]

In view of Hancock's comments, we have repeated our calculations [8,11] of plots of steric energy against M–N distance for the macrocycle L but now with a range of different values of k_s. We discuss here the results obtained for $[\mathrm{CoLCl}]^{2+}$ (similar results were obtained for $[\mathrm{FeLCl_2}]^{+}$ and $[\mathrm{CuL}]^{2+}$ also).

In $[\mathrm{CoLCl}]^{2+}$, the macrocycle folds to occupy five sites of an octahedron around the cobalt atom with N(3), N(6), N(9), and N(12) in the equatorial plane and N(15) axial (and in a position *trans* to the chlorine atom). We have minimised the steric energy for values of r_0 in steps of 0.01 Å from 1.90 to 2.10 Å using k_s = (*a*) 25.0, (*b*) 2.5, and (*c*) 1.0 mdyn Å^{-1}. All other parameters were identical to those used previously.[8,11,*] The three resulting curves are shown in Figure 2. We estimate the minima in energy for these curves to be at r_0 = 2.011, 2.007, and 1.985 Å respectively. These differences are quite small but significant and there are major variations in the total steric energies (31.74, 30.09, and 28.12 kcal mol^{-1} respectively) and in the individual M–N distances and these are given for each minimum in the Table. We also use Busch's method [3] of allocating a value for k_s = 0.0 mdyn A^{-1} and the results are also included.



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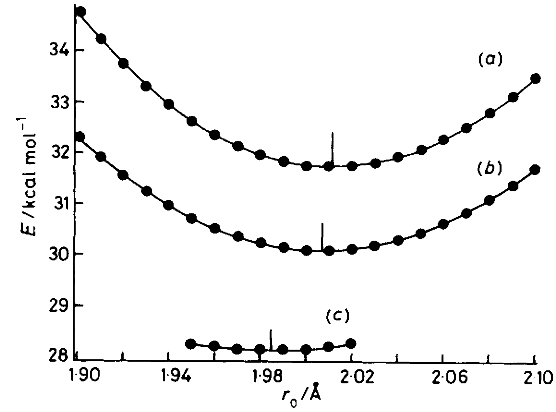

Figure 2. Plot of steric energy (E/kcal mol^{-1}) for $[\mathrm{CoLCl}]^{2+}$ against r_0 with k_s = (*a*) 25.0, (*b*) 2.5, and (*c*) 1.0 mdyn Å^{-1}. Other parameters in the force field are listed in refs. 8 and 11; estimated minima are shown as vertical lines

We contend that these results justify our method. By using a large value of k_s, 25.0 mdyn Å^{-1}, the macrocycle is forced into a conformation that will fit all the M–N bond lengths to r_0. By using the smaller values of k_s, 2.5, 1.0, or 0.0 mdyn Å^{-1}, the M–N bond stretch term becomes less important relative to terms that relate to the macrocycle conformation alone. Thus the steric energy of the cations drops considerably as k_s is decreased, from 31.74 kcal mol^{-1} at k_s = 25.0 mdyn A^{-1} to 18.94 kcal mol^{-1} at k_s = 0.00 mdyn A^{-1}. This is because the macrocycle can adopt a lower energy conformation when the M–N lengths are allowed (by a low k_s value) to vary; in the extreme case of k_s = 0.0 mdyn Å^{-1} it adopts a conformation with an energy lower by 12.80 kcal mol^{-1}, albeit with an unrealistic set of bond lengths ranging from 1.48 to 2.36 Å.[†]

These results show that the statement in Hancock's Letter, that the minimum in such a curve (point A in Figure 1) is fixed with respect to both axes irrespective of the value of k_s used, is not generally valid. We have obtained variations with k_s in hole size (as measured by the minimum in the curves of Figure 2) and also in the value of total steric energy.

It is possible that for macrocycles with a more symmetrical

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[*] The curve for k_s = 1.0 mdyn Å^{-1} is incomplete because at $r_0 < 1.95$ Å the structure could not be refined using MM2. This is because the MM2 program uses a cubic stretch term for bond lengths and when r becomes different from r_0 by $\geqslant$ *ca.* 0.3 Å, V_r becomes large and negative and as a consequence the molecule 'falls apart.' In this case, the value of k_s was not large enough to stop this happening because the lowest energy conformation of the macrocycle has a wide range of bond lengths which differ by >0.3 Å from r_0 (see Table).

[†] In the crystal structure of $[\mathrm{CoLCl}]^{2+}$, bond lengths are Co–N(3) 2.001, Co–N(6) 1.812, Co–N(9) 1.934, Co–N(12) 1.929, Co–N(15) 1.908 Å. Besides showing that the Co atom is a poor fit to the macrocycle hole, these values indicate that some variation in M–N distances is likely in metal complexes of L. We showed [8,11] that it was possible to predict these variations in Co–N distances to within 0.03 Å using k_s 2.25 mdyn Å^{-1}, cubic stretch term,[12] c_s = −2.00 Å^{-1}, and r_0 = 1.88 Å. Because the variations in M–N distances are so dependent upon the values of k_s used, we decided in our method for the calculation of hole size to fix all M–N distances at the same value, though we outline a possible method to take account of variations in refs. 8 and 11.

Table. Parameters of the conformations of $[CoLCl]^{2+}$ at the energy minima obtained with differing values of k_s (all energies in kcal mol^{-1})

	(*a*)	(*b*)	(*c*)	(*d*)*
k_s/mdyn Å^{-1}	25.0	2.5	1.0	0.0
r_0/Å (at minimum energy)	2.011	2.007	1.985	—
Individual M–N bond lengths (Å) from the structures with minimum energy at the above r_0				
M–N(3)	2.016	2.059	2.134	2.359
M–N(6)	2.002	1.940	1.869	1.478
M–N(9)	2.012	2.016	2.005	2.011
M–N(12)	2.012	2.023	2.032	2.255
M–N(15)	2.014	2.036	2.061	2.244
Total energy	31.74	30.09	28.12	18.94
Contributing energies				
Compression energy	3.28	4.11	4.97	1.54
Bending energy	19.31	17.49	15.64	16.62
Stretch–bend energy	0.72	0.74	0.47	−1.56
Van der Waals energy				
for 1,4 interactions	10.72	10.46	10.24	9.39
for other interactions	−3.96	−4.11	−4.23	−4.85
Torsional energy	0.98	0.87	0.67	−0.51
Dipole energy	0.69	0.56	0.35	−1.70

* For (*d*) no value of r_0 was input. The structure refined to give the M–N distances quoted.

donor set and rigid geometry than L, variations in k_s may not affect calculations of hole size and indeed Hancock has shown that for cyclam variations in k_s make little difference. However, for macrocycles that can adopt various conformations, and which contain donor atoms are different in type and/or position in the co-ordination sphere, we consider our method to be preferable.

Hancock quotes values for k_s of 0.68 up to 2.25 mdyn Å^{-1} for various metals as if these were known and accepted values for force constants. These appear to be spectroscopic force constants but there is no intrinsic reason why these should be used without question in molecular mechanics calculations.[13] It has been the experience of those involved in using molecular mechanics for organic molecules that all parameters need to be continually adjusted to get the best fit between theory and experiment. Hancock implies that his curves are correct because he uses the correct values for the parameters in the force field. We do not claim this and indeed our method makes a virtue of the necessity of not knowing the parameters of metal atoms with any accuracy. The optimisation of parameters in a force field for metal complexes is at a very preliminary stage.

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Received 3rd *December* 1985; *Paper* 5/2114