Nuclear Magnetic Resonance Study of the Association between Adamantanone and the Shift Reagent Eu(fod)$_3$

Alena Horská and Milan Hájek *
Laboratory of Synthetic Fuels, Prague Institute of Chemical Technology, 166 28 Prague 6, Czechoslovakia
Petr Trška
Department of Organic Chemistry, Prague Institute of Chemical Technology, 166 28 Prague 6, Czechoslovakia

The association of Eu(fod)$_3$ (L) to adamantanone (S) in CDCl$_3$ was studied by ^{1}H n.m.r. spectroscopy. From the concentration dependence of the induced shifts the bound shifts were obtained by an optimization procedure and a gradient method. The equilibrium constants for the formation of complexes LS, LS$_2$, and LS$_3$ were calculated. The best fit was found for the two-step association LS,LS$_2$ with association constants K_{11} 63 dm^3 mol^{-1} and K_{12} 514 dm^3 mol^{-1}. The position of europium in the complex adduct was studied by one- and four-site binding models and both results were statistically compared.

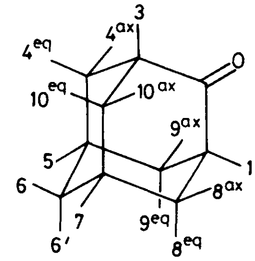
Chemical shifts which are induced by the addition of lanthanide shift reagents (LSR) can be used for the calculation of the so-called bound shifts which are related to the molecular structure by the McConnell equation.[1] The simplified form of this equation is (1) where Δ^i is the bound shift, k is a constant, and

$$\Delta^i = k\,(3\cos^2\theta_i - 1)/r_i^3 \qquad (1)$$

r_i and θ_i are parameters characterizing the position of the ith atom in the complex adduct.

Various methods have been proposed for the calculation of the bound shifts and their advantages and disadvantages have been discussed.[2] Experimentally, all methods are based on the observation of the concentration dependence of the induced shifts.

This paper is devoted to a comparison of the optimization and gradient methods for the bound shift calculation. Adamantanone (**1**) was used as the substrate and bound shifts obtained were compared with published data in terms of one- and four-site co-ordination models.



(1)

Experimental

Adamantanone was prepared according to the procedure described.[3] The lanthanide shift reagent Eu(fod)$_3$ (Merck) was sublimed (0.05 Torr; 140 °C) and stored over P$_2$O$_5$ prior to use. CDCl$_3$ (Merck) was used as solvent with 2% tetramethylsilane as internal standard. The solvent was dried with 4 Å molecular sieves. ^{1}H N.m.r. spectra were measured at 100 MHz on a Tesla BS 567 Fourier transform spectrometer with an internal deuterium lock at 29.7 ± 1 °C. All computations were performed on an ADT 43 16 minicomputer.

The induced shifts of adamantanone were obtained by the following methods: (a) weighted amounts of Eu(fod)$_3$ were added to a 0.15M solution of (**1**) (0.5 ml) in CDCl$_3$; (b) a 0.3M solution of adamantanone was added to the weighed amount (0.3 g) of Eu(fod)$_3$. Induced shifts were measured in the concentration range characterized by the molar ratio R_p 0.05—2.5 (R_p is the molar ratio L$_o$/S$_o$ where L$_o$ and S$_o$ are the total concentrations of the shift reagent and substrate, respectively). The density of the solution of Eu(fod)$_3$ and adamantanone was considered to be equal to the density of CDCl$_3$ as shown by density measurements.

The bound shifts Δ^i_{jk} were obtained by optimization[4] and gradient methods[5] (as the slope of the plot of δ^i_{obs} *versus* R$_p$). The calculation of bound shifts was performed by the KONST program[6] which is based on the solutions of equation (2) where

$$\delta^i_{ind} = \sum_{j=0}^{m}\sum_{k=0}^{n} k\,\Delta^i_{jk}\,K_{jk}[L]^j\,[S]^k \qquad (2)$$

K_{jk} is the equilibrium constant. The equilibrium concentrations [S] and [L] were calculated by a method developed by Perrin *et al.*[7] The computation is controlled by comparison of the optimization criterion F [equation (3)] where N is the number

$$F = \sum_{i=1}^{N}\sum_{l=1}^{M} (\delta^i_{obs} - \delta^i_{calc})^2 \qquad (3)$$

of observed signals in the molecule of substrate and M is the number of LSR concentrations. The KONST program was written in FORTRAN and is available from the authors.

The position of europium in the complex adduct was calculated by the PSEUDO 1980 program[8] which is a four-parameter optimization program for the solution of the pseudo-contact equation (1). The Hamilton agreement factor R[9] was used as the optimization criterion [equation (4)] where δ^i_{obs}

$$R = [\Sigma(\delta^i_{calc} - \delta^i_{obs})^2/\Sigma(\delta^i_{obs})^2]^{\frac{1}{2}} \qquad (4)$$

and δ^i_{calc} are the calculated and observed bound shifts, respectively. The force field calculation of the adamantanone co-ordinates was performed with the MM2 program.[10]

Results and Discussion

The bound shift Δ_{11} corresponding to the induced shift of the substrate totally complexed in the adduct LS can be calculated by solution of the equilibrium system LSR–substrate described by equations (5). The bound shift can be obtained from equa-

$$L + S \rightleftharpoons LS \quad (5a)$$

$$L + 2S \rightleftharpoons LS_2 \quad (5b)$$

$$2L + S \rightleftharpoons L_2S \quad (5c)$$

$$mL + nS \rightleftharpoons L_mS_n \quad (5d)$$

$$K_{11} = [LS]/[L]\,[S] \quad (6a)$$

$$K_{12} = [LS_2]/[L]\,[S]^2 \quad (6b)$$

$$K_{21} = [L_2S]/[L]^2\,[S] \quad (6c)$$

$$K_{mn} = [L_mS_n]/[L]^m\,[S]^n \quad (6d)$$

$$S_o = [S] + [LS] + 2[LS_2] + \cdots [L_2S] \cdots + n[L_mS_n] \quad (7)$$

$$L_o = [L] + [LS] + [LS_2] + \cdots 2[L_2S] \cdots + m[L_mS_n] \quad (8)$$

tions describing the dependence of the induced shifts δ^i_{ind} on the concentration of the lanthanide shift reagent and substrate[4] [equation (9)] where δ^i_{exp} is the observed chemical shift in the

$$\delta^i_{ind} = \delta^i_{exp} - \delta^i_o = \sum_{k=1}^{n} \sum_{j=1}^{m} k[L_jS_k]\,\Delta^i_{jk} \quad (9)$$

presence of the shift reagent and δ^i_o is the chemical shift of the free substrate. The only method which enables the numerical solution of equations (6)—(9) is an optimizing procedure[4] provided that the values of m and n together with the values of the experimental induced shifts and the total concentrations of substrate and lanthanide shift reagent are known. Three association mechanisms were taken into consideration: (i) one-step association (LS; $n = m = 1$); (ii) two-step association (LS,L_2S; $n = 1$, $m = 1,2$); (iii) two-step association (LS,LS_2; $n = 1,2$, $m = 1$); (iv) three-step association (LS,LS_2,LS_3; $n = 1,2,3$, $m = 1$). The dimerization of the lanthanide shift reagent can also influence the equilibrium condition but it has been found previously that the formation of the dimer L_2 of Eu(fod)$_3$ can be neglected in $CDCl_3$.[11] In Figure 1 the experimental induced shifts of adamantanone (signals for H-1 and H-3) are compared with those calculated for one-step (i), two-step (ii, iii), and three-step (iv) equilibria. The deviations between experimental δ^i_{obs} and calculated δ^i_{calc} induced shifts described by the optimization criterion F are much greater for the formation of complexes LS and LS,L_2S than for the two-step LS,LS_2, and three-step mechanism, LS,LS_2LS_3, respectively (see Table 1). The comparison of the optimization criteria for two- and three-step association supports the fact that only the formation of LS

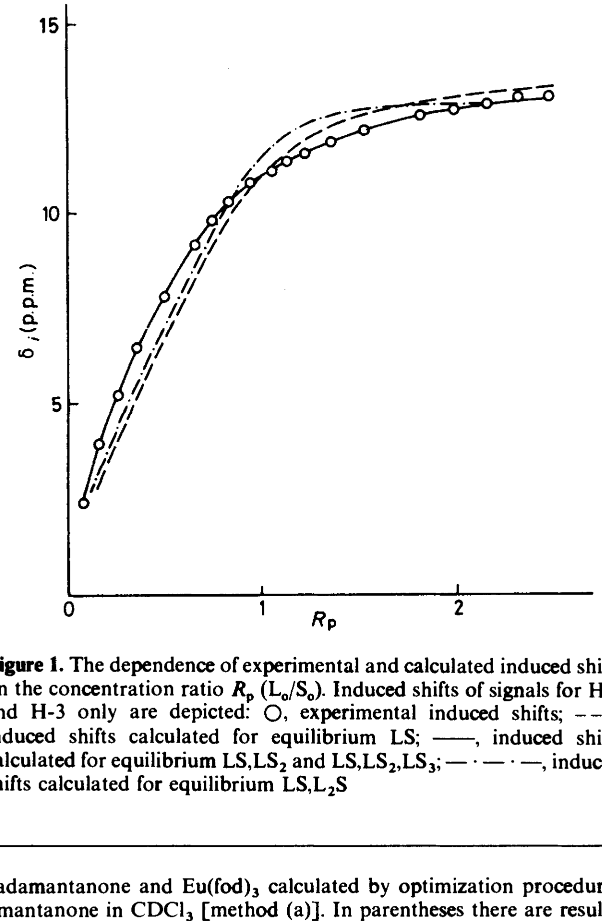


Figure 1. The dependence of experimental and calculated induced shifts on the concentration ratio R_p (L_o/S_o). Induced shifts of signals for H-1 and H-3 only are depicted: ○, experimental induced shifts; – – –, induced shifts calculated for equilibrium LS; ——, induced shifts calculated for equilibrium LS,LS_2 and LS,LS_2,LS_3; — · — · —, induced shifts calculated for equilibrium LS,L_2S

Table 1. ^1H Bound shifts Δ^i_{jk} and values of equilibrium constants between adamantanone and Eu(fod)$_3$ calculated by optimization procedure. Experiments were carried out by addition of Eu(fod)$_3$ to the solution of adamantanone in $CDCl_3$ [method (a)]. In parentheses there are results calculated for experimental data obtained by addition of the solution of adamantanone to weighted amount of Eu(fod)$_3$ [method (b)]. The values of bound shifts and equilibrium constants are an average value of two measurements

	LS	LS,L_2S		LS,LS_2		LS,LS_2,LS_3		
Atom	Δ_{11}	Δ_{11}	Δ_{21}	Δ_{11}	Δ_{12}	Δ_{11}	Δ_{12}	Δ_{13}
1,3	12.56	14.54	5.10	13.11	12.30	13.06	11.90	11.10
	(14.19)	(11.02)	(17.80)	(13.98)	(4.00)	(13.80)	(6.00)	(4.80)
$4^{ax},8^{ax},9^{ax},10^{ax}$	6.52	7.47	2.80	6.92	5.90	6.76	5.80	4.80
	(7.14)	(5.54)	(9.40)	(7.21)	(1.90)	(7.05)	(2.80)	(2.20)
$4^{eq},8^{eq},9^{eq},10^{eq}$	4.22	4.82	1.60	4.54	3.80	4.30	4.10	3.50
	(4.60)	(3.64)	(5.70)	(4.54)	(1.50)	(4.44)	(2.10)	(1.70)
5,7	3.72	4.25	1.30	3.67	3.90	3.75	3.60	3.50
	(4.05)	(3.34)	(4.00)	(3.86)	(1.20)	(3.94)	(1.50)	(1.00)
6,6′	2.98	3.48	1.20	3.22	2.90	3.26	2.10	3.10
	(3.31)	(2.80)	(3.10)	(3.22)	(1.00)	(3.22)	(1.40)	(1.10)
K_{jk}[a]	174.6	92.1	197.9	50.8	605.5	64.3	431.8	1 190.0
	(21.5)	(113.9)	(170.1)	(62.6)	(513.8)	(57.7)	(433.5)	(2 080.0)
F[b]	29.2	22.1		0.33		0.49		
	(27.1)	(24.7)		(1.32)		(0.38)		

[a] Equilibrium constants ($mol^{-1}\ dm^3$). [b] Optimization criterion.

Table 2. The results of the optimization of the position of Eu in complex adduct adamantanone–Eu(fod)$_3$ obtained for one-site co-ordination model. ^{1}H Relative bound shifts Δ_{11} calculated by optimization method (two-step association LS,LS$_2$) and gradient method were used

Atom	Optimization method[a] (a)	Optimization method[a] (b)	Gradient method[a] (a)	Gradient method[a] (b)
1,3	4.08	4.34	4.20	4.23
$4^{ax},8^{ax},9^{ax},10^{ax}$	2.15	2.24	2.10	2.14
$4^{eq},8^{eq},9^{eq},10^{eq}$	1.41	1.41	1.32	1.37
5,7	1.14	1.20	1.14	1.17
6,6′	1.00	1.00	1.00	1.00
$r_{\text{Eu-O}}$[b]	0.23	0.22	0.22	0.22
R(%)[c]	3.4	5.1	5.6	5.5

[a] See Experimental section for method (a) and (b). [b] $r_{\text{Eu-O}}$ distance between Eu and O atoms in complex adduct, the optimized position lies on the extension of C=O bond. [c] Hamilton agreement factor.[9]

and LS$_2$ complexes plays an important role for the Eu(fod)$_3$–adamantanone system. The increasing number of complex particles considered for the calculation do not improve the optimization criterion, although the data set is statistically very well determined (125 experimental points, 6 unknown parameters for one complex particle).

Table 1 also summarizes the values of calculated bound shifts and association constants obtained by optimization procedure for experimental methods (a) and (b) (see Experimental section). A comparison of equilibrium constants calculated from both sets of experimental data shows that the equilibrium constants K_{11} for the formation of LS complexes are equal within the range of experimental error only in the cases where two-step (LS,LS$_2$) and three-step (LS,LS$_2$LS$_3$) associations are supposed. These results also support the presence of the LS$_2$ adduct in CDCl$_3$ solutions of adamantanone and Eu(fod)$_3$.

Raber *et al.*[12] have found an equilibrium constant K_{11} between adamantanone and Eu(fod)$_3$ in CDCl$_3$ of 316 dm^3 mol^{-1} which is five times greater than the constant calculated by us. This difference can be reconciled because different experimental conditions on the one hand and optimization procedures on the other could be responsible for such a deviation. Our experience is that a change of the value of the association constant of *ca.* 5% (absolute) can change the optimization criterion by 100%, but the ratio of calculated bound shifts stays constant within 5% (relative).

From the practical point of view the bound shifts are more important than the association constants because they are used for the solution of the McConnell equation. Our bound shifts and those published differ by *ca.* 5% (relative).

In Table 2 relative values of the bound shifts Δ_{11} obtained by the optimization method and by the gradient method for LS,LS$_2$ association are compared. Analysis of the calculated data shows that there are small differences of *ca.* 3% between the values obtained by optimizing and gradient methods. In spite of the fact that the gradient method was derived only for a one-step association mechanism the agreement between the two methods is very good. Shapiro[4] has shown that the initial slope for a plot of δ^i_{ind} against R_p is $2\Delta_{12}$ for $S_o \geqslant L_o$. This was not proved by our results but the explanation can be found in the experimental error of the calculation of the bound shifts Δ_{12} which is very high compared with the error in Δ_{11}.

Good agreement between the relative bound shifts calculated by the optimizing procedure and by the gradient method can be explained theoretically. For two-step association (LS,LS$_2$) δ^i_{ind} is given by equation (10).[13] For this case equation (9) can be rewritten as (11) and for the limiting condition $R_p \longrightarrow 0$ the concentration $[S] \longrightarrow S_o$ and the initial value of the slope of a plot of δ^i_{ind} against R_p is given by the equation (12). The relative bound shift of the ith atom obtained by gradient method has the form (13) where Δ^i_{grad} and Δ^k_{grad} are bound shifts calculated by the gradient method. If equation (14) holds then equation (13) can be transformed into (15) where δ^i_{ind} and δ^k_{ind} are induced shifts of ith and kth protons. It was found that the relative induced shifts of adamantanone were constant [*e.g.* equation (15)] within experimental error in the measured concentration range (see Figure 2). According to this experimental result we may suppose that the real ratio $\Delta^i_{11}/\Delta^i_{12}$ is equal for all protons and the agreement between the results for gradient and two-step optimization procedures can be explained. This result also shows that the relative error of the calculation of the bound shift Δ_{12} is higher than the error of the calculation of Δ_{11}.

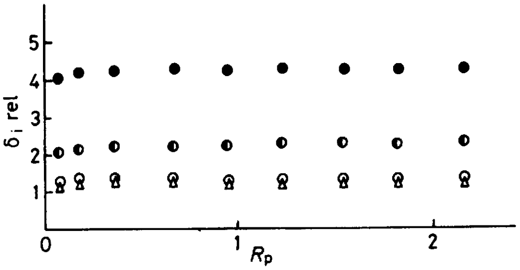


Figure 2. The dependence of relative induced shifts of adamantanone on the concentration ratio R_p (L_o/S_o); induced shifts of H-6 and H-6′ were equal to 1.00: Relative induced shifts are denoted as follows: ●, H-1,H-3; ◐, H-4^{ax},H-8^{ax},H-9^{ax},H-10^{ax}; ○, H-4^{eq},H-8^{eq},H-9^{eq},H-10^{eq}; △, H-5, H-7

$$\delta^i_{\text{ind}} = 2\,R_p\Delta_{12} + \frac{[\text{LS}]}{S_o}\left(\Delta_{11} - 2\,\Delta_{12}\frac{1 + K_{11}\,[\text{S}]}{K_{11}\,[\text{S}]}\right) \quad (10)$$

$$\delta^i_{\text{ind}} = R_p\,\frac{\Delta_{11}K_{11}\,[\text{S}] + 2\,\Delta_{12}K_{12}\,[\text{S}]^2}{1 + K_{11}\,[\text{S}] + K_{12}\,[\text{S}]^2} \quad (11)$$

$$\left(\frac{d\,\delta^i_{\text{ind}}}{d\,R_p}\right)_{R_p \longrightarrow 0} = \Delta_{\text{grad}} = \frac{\Delta_{11}K_{11}\,S_o + 2\,\Delta_{12}K_{12}\,S_o^2}{1 + K_{11}\,S_o + K_{12}\,S_o^2} \quad (12)$$

$$\frac{\Delta^i_{\text{grad}}}{\Delta^k_{\text{grad}}} = \frac{\Delta^i_{11}K_{11}\,S_o + 2\,\Delta^i_{12}K_{12}\,S_o^2}{\Delta^k_{12}K_{11}\,S_o + 2\,\Delta^k_{12}K_{12}\,S_o^2} \quad (13)$$

$$\Delta^i_{11}/\Delta^i_{12} = \Delta^k_{11}/\Delta^k_{12} = \text{const} \quad (14)$$

$$\Delta^i_{\text{grad}}/\Delta^k_{\text{grad}} = \Delta^i_{11}/\Delta^k_{11} = \delta^i_{\text{ind}}/\delta^k_{\text{ind}} \quad (15)$$

The bound shifts obtained were used for the optimization of the geometry of the complex adduct. Adamantanone is a typical case of a small symmetrical molecule which gives, from a statistical point of view, a poorly determined base of variables for LSR experiments (the number of non-equivalent atoms in the molecule). This base is poorly determined as in the data base composed from ^{1}H bound shifts (five variables) and the ^{1}H and ^{13}C bound shifts (ten variables), if for each unknown parameter, which is calculated, five independent variables are required. At the present time one-, two- and four-site co-ordination models of adamantanone to the shift reagent have been studied and compared using proton and carbon-13[14] bound shifts. The PSEUDO 1980 program was adopted both for one-site co-ordination of Eu(fod)$_3$ to adamantanone and for the four-site binding model.[14] Table 2 summarizes the calculated distances of Eu to O ($r_{\text{Eu-O}}$) which were 0.22—0.24 nm along the axis of

Table 3. The results of the optimization of the position of Ln in complex adduct adamantanone–Ln(fod)$_3$ obtained for four-site co-ordination model. ^{1}H Relative bound shifts were taken from refs. 14, 16, and 17 and from Table 2 (optimization method)

Atom	[a] I	[b] II	[c] III	[d] IV	[d] V
1,3	4.49	4.27	4.21	4.08	4.34
$4^{ax},8^{ax},9^{ax},10^{ax}$	2.28	2.21	2.21	2.15	2.24
$4^{eq},8^{eq},9^{eq},10^{eq}$	1.40	1.39	1.41	1.41	1.41
5,7	1.13	1.19	1.18	1.14	1.20
6,6′	1.00	1.00	1.00	1.00	1.00
Ln	Yb	Eu	Eu	Eu	Eu
solvent	CCl_4	CCl_4	CCl_4	$CDCl_3$	$CDCl_3$
$r_{Ln\text{-}O}$/nm [e]	0.28	0.29	0.29	0.29	0.28
α [f]	32.1	28.6	28.0	29.3	29.8
β [f]	28.3	24.1	31.6	10.1	24.3
R(%) [g]	0.5	1.3	1.3	0.8	1.0

[a] Ref. 14. [b] Ref. 16. [c] Ref. 17. [d] See Table 2. [e] $r_{Ln\text{-}O}$ the distance between lanthanide atom and oxygen in complex adduct. [f] See Figure 3. [g] Hamilton agreement factor.[9]

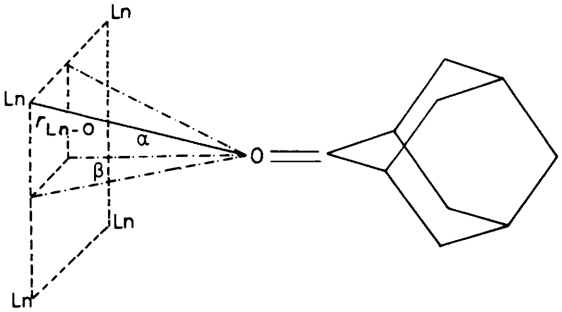


Figure 3. Four-site model of the co-ordination of the shift reagent to adamantanone. Lanthanide ion (Ln) is located in the plane perpendicular to the C=O bond. The Ln-position is described by angles α, β and the distance between Ln and oxygen atom (r_{Ln-O})

the C=O bond for the one-site model. This distance is in very good agreement with X-ray data[15] ($r_{Eu\text{-}O}$ 0.23—0.24 nm). The Hamilton agreement factor R is 3.4—5.6%. The lowest value of R was obtained by experimental method (a) assuming a two-step association mechanism.

The agreement factor R decreased to 0.7—1.6% if the calculation was performed without the bound shift of H-1 and H-3. This can be accounted for by both decreasing the number of variables in the calculation and by the possible influence of the contact shifts which are sometimes supposed to be important for atoms close to the co-ordination site.[11] The relative difference between calculated and experimental bound shifts was greatest for H-1 and H-3.

Chadwick *et al.*[14] have proposed a multi-site co-ordination model for the co-ordination of LSR to the carbonyl group. For adamantanone they suggested a four-site co-ordination model (Figure 3) characterized by four equally populated co-ordination centres which are symmetric in relation to the two symmetry planes of adamantanone. In Table 3 results of the optimization for four-site binding model calculated by the PSEUDO 1980 program of our and others' experimental data[14,16,17] are presented. The position of Eu obtained by the PSEUDO 1980 program is very close to that calculated by Chadwick although ^{1}H bound shifts only were used. The distance between Eu and O is greater than in the case of the one-site model. The agreement factors are in the range 0.5—1.3% which is much better than for the one-site co-ordination model. If H-1 and H-3 were excluded from the calculation the position of the Eu atom was found 0.35 nm from the oxygen atom (R 0.05%).

The comparison of four- and one-site co-ordination models by the Hamilton R-factor test[9] indicates that at the 95% confidence level the one-site co-ordination model can be rejected because the ratio of R factors is higher than the critical value ($R_{4,10,0.05}$ 1.546).

Although the statistical test prefers the four-site co-ordination model, this cannot be accepted without comment. First, from the physical point of view the one-site model which describes the co-ordination of the carbonyl group in terms of a linear carbonyl σ-bond interaction with the 5d orbitals of Eu[16] seems to be the most reliable co-ordination model. Second, if different experimental sets of bound shifts are compared by using the Hamilton R-test, the same results can be obtained for the one-site as for the four-site co-ordination model. We tested the data sets obtained by experimental methods (a) and (b). For the one-site co-ordination model the ratio $R(b)/R(a) = 1.47$ and for the four-site co-ordination model $R(b)/R(a) = 1.42$ was found. From statistical point of view both treatments are indistinguishable and the adoption of the four-site model brings no advantage. Further it is obvious that the use of the four-site model is restricted to compounds having similar symmetry to that of adamantanone. In the case of less symmetric molecules the number of optimized parameters would have to be increased to a great extent (the population of binding sites may not be equal and/or the position of binding sites may not be symmetric) compared with the number of variables.

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