Molecular Determinants for Drug–Receptor Interactions. Part 5.† Anisotropic and Internal Motions in Analgesic Narcotics (Morphine, Oxymorphone) and Related Antagonists (Nalorphine, Naloxone) by Carbon-13 Nuclear Magnetic Resonance Spin–Lattice Relaxation Times

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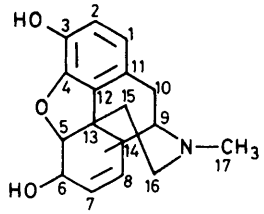
Carbon-13 n.m.r. spin–lattice relaxation times (T_1) were measured for two pairs of related agonist–antagonist narcotic analgesics, morphine–nalorphine and oxymorphone–naloxone, in $(CD_3)_2SO$–$CDCl_3$ solution. The experimental T_1 values were interpreted using a model of anisotropic reorientation of a rigid body. Fitting procedures provided the parameters of the overall molecular motion (diffusion coefficients and Eulerian angles) for each compound. Additional calculations were made by assuming a model of anisotropic reorientation of a rigid body with overimposed internal motions of the flexible *N*-methyl and *N*-allyl groups. This model was adequate to reproduce also the relaxation times of the carbon atoms undergoing internal free rotation. The motional parameters indicate a smaller rotational diffusion rate for the *N*-allyl fragment of naloxone as well as for the whole molecule with respect to the other compounds. The *N*-methyl group of the morphine molecule rotates at a greater rate than the same group in oxymorphone or the *N*-allyl moieties in the remaining molecules.

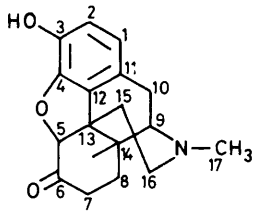
In clinical practice an important feature of opiate pharmacology is the fast and complete reversal of morphine-like (agonist) effects upon injection of naloxone or other opiate antagonists. In general, narcotic antagonists are defined as compounds that determine withdrawal in narcotic addicts and reverse or prevent the analgesic effect of narcotics.[1] The key feature of agonistic–antagonistic activity appears to reside in the nature of the alkyl substituent on the piperidine nitrogen. For example, replacement of the methyl group on the nitrogen of morphine (**1**) and oxymorphone (**2**) by an allyl group changes the pharmacological activity of the agonist to that of a mixed narcotic agonist–antagonist [nalorphine (**3**)] or a pure antagonist [naloxone (**4**)], respectively. The problem thus arises of how opiates of such similar structures can produce entirely opposite effects *in vivo*.

The observed differential effect of sodium on receptor binding of opiate agonists and antagonists has previously been interpreted in terms of induced changes of the conformation of the receptor sites.[2] The idea that the opiate receptor is a membrane-bound complex, in which an important role is played by phospholipids and proteins, has also been suggested on the basis of differential effects observed upon enzymic treatment.[3]

Relaxation times in n.m.r. spectrometry have been found to be useful probes for the investigation of molecular structure, conformation, conformational dynamics, internal motions, and molecular interactions.[4] This method thus appears potentially well suited to initiate understanding, at the molecular level, of how and to what extent a narcotic (agonist or antagonist) can interact with the putative receptor. However, such an approach can be envisaged only if the motional features of the active



(1)



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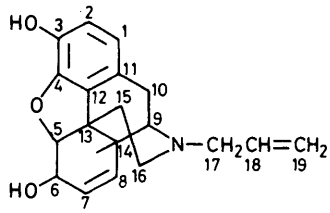

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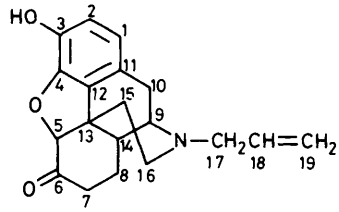

(4)

† Part 4, G. C. Pappalardo, A. Grassi, M. Nicolini, and H. Lumbroso, *Z. Naturforsch., Teil B*, 1984, **39**, 1156.

molecules are known. The main objective of the present work was to obtain information on the motional characteristics in solution of the molecules (**1**)—(**4**), by using carbon-13 n.m.r. spin–lattice relaxation times.

Experimental

Carbon-13 n.m.r. spectra were obtained at 25.16 MHz using a disk-augmented Varian XL-100/15 Fourier transform instrument equipped with high power pulse amplifier (pulse length for $\pi/2$ flip angle: 13 μs).

Compounds (**1**)—(**4**) were purchased as hydrochloride salts. The free bases were obtained by mild alkaline treatment (NH_4HCO_3) of the salts dissolved in water and subsequent extraction with an organic solvent ($CDCl_3$). The purity of the free bases was attested by their n.m.r. (^1H and ^{13}C) spectra. A mixture of $(CD_3)_2SO$ and $CDCl_3$ (1:1) was used as solvent in order to collect the spectral data in the same medium for all compounds. The solutions were 5—10% w/v, according to the solubility of the samples. Each solution was degassed prior to the experiment. The chemical shifts quoted in Table 1 are relative to internal Me_4Si. Assignments of carbon resonances were made by standard Fourier transform n.m.r. methods, and are based on chemical shift considerations, off-resonance multiplicities and, in some instances, correlations between proton and carbon-13 spectra.

Longitudinal relaxation times (T_1) were measured at 308 K by the inversion–recovery method.[5] To improve the accuracy of the signal intensity measurements, time-domain signals were acquired in large (22 to 24 K) data tables and were exponentially filtered to give line widths of 10 Hz after Fourier transformation. Typically 12—16 samples of the recovery magnetizations were taken. These were then subjected to three-parameter non-linear least-squares analysis to yield T_1 data. Error analyses attest that the relative error in T_1 values for a given experiment is within 2%. The overall accuracy of T_1 data collected in Table 1 is estimated to be within ±5%.

Theory and Computational Techniques

To analyse the measured T_1 values of compounds (**1**)—(**4**), a model of anisotropic reorientation of a rigid body was assumed. The extended relaxation equation[6] for such a model was developed and employed for the fitting of the experimental T_1 data, assuming a diffusion model for reorientation and a dipole–dipole mechanism for relaxation. The equation applies under conditions of rapid molecular reorientation and in the extreme narrowing limit ($\omega\tau_c \ll 1$). For a given C–H bond the inverse relaxation time is proportional to $Q(\theta_i,\psi_i,\rho_1,\rho_2)$. Equation (1)

$$Q(\theta_i,\psi_i,\rho_1,\rho_2) = (4 + \rho_1 + \rho_2)\cos^2\theta_i + \left[(1 + 4\rho_1 + \rho_2)\cos^2\psi_i + (1 + 4\rho_2 + \rho_1)\sin^2\theta_i - (\rho_1 - \rho_2)^2\frac{9}{4 + \rho_1 + \rho_2}\sin^2\psi_i\cos^2\psi_i\right]\sin^2\theta_i - \left[(\rho_1 - \rho_2)^2\frac{9\cos^2\psi_i}{1 + \rho_1 + 4\rho_2} + (1 - \rho_2)^2\frac{9\sin^2\psi_i}{1 + 4\rho_1 + \rho_2} - (\rho_1 - \rho_2)^2\frac{9\sin^2\psi_i\cos^2\psi_i}{4 + \rho_1 + \rho_2}\right]\cos^2\theta_i\sin^2\theta_i \quad (1)$$

can be easily obtained from the general expression for the inverse nuclear relaxation time for an asymmetric rotor. Here θ and ψ are the polar and azimuthal angles that fix the direction of a C–H vector with respect to the reference system in which the diffusion tensor is diagonal. D_1, D_2, D_3 are the corresponding eigenvalues that in equation (1) appear as $\rho_1(=D_1/D_3)$ and $\rho_2(=D_2/D_3)$. The function F to be minimized is given by equation (2), whereby we fit the ratios to the various T_1 values.

$$F = \sum_i\left[\frac{T_1}{T_i} - \frac{Q(\rho_1,\rho_2;\theta_i,\psi_i)}{Q(\rho_1,\rho_2;\theta_1,\psi_1)}\right]^2 \quad (2)$$

The overall factor of the theoretical T_1 values was then adjusted in order to minimize the absolute square of the deviation.

The T_1 data were analysed by means of two computer programs on a CDC 7600 system. The first routine (INERTIA),[7] using appropriate molecular geometry,* calculates the co-ordinates of atoms, the moment of intertia tensor, the direction cosines of the principal axes, and the principal moments of inertia. The same program produces, from the calculated data, the $\sin^2$ values of the associated polar and azimuthal angles between the relevant C–H vectors and the moment of inertia axes. The final step of the computations utilized the program MINSQ,[12] which finds the minimum of a sum of squares of functions for a set of input parameters.

The approximation that the principal axes of the moment of inertia tensor and the rotational diffusion tensor coincide was shown to be of limited validity for polar molecules and was therefore avoided. Therefore the three Euler angles (α, β, γ) were treated as adjustable parameters, which increased the number of fitting variables to six. Angles α, β, γ relate the principal axis system (A, B, C) of the moment of inertia tensor to the new principal axis system (A', B', C') of the rotational diffusion tensor.†

The fitting procedure consisted of the optimization of the diffusion coefficent ratios, first with $\alpha = \beta = \gamma = 0°$, and a large set of starting values; optimization was repeated for several combined sets of Eulerian angles with 10° steps. The best value of the physically meaningful minima was selected by an appropriate routine.

To obtain the relaxation parameters for the *N*-alkyl carbon atoms, the computations were extended to include the internal rotations about the N–C(17) and C(17)–C(18) bonds. By following Levine's treatment,[13] the spectral density function at the zero frequency of the ith side chain carbon atom is expressed, with Levine's convention for the angles, by equation (3) where $\eta^2_{mr} + \zeta^2_{mr}$ is defined by equation (4), E_m denotes the

$$J(0) = \sum_{m,r,s,a,\cdots p}\left[\eta^2_{mr}(\alpha,\beta) + \zeta^2_{mr}(\alpha,\beta)\right] \times \frac{1}{E_m + r^2D_{i(1)} + s^2D_{i(2)} + \cdots p^2D_{i(n)}} \times \left|d_{rs}(\beta_1)\right|^2 \cdot \left|d_{sa}(\beta_2)\right|^2 \cdots \left|d_{p0}(\beta_n)\right|^2 \quad (3)$$

$$\eta^2_{mr} + \zeta^2_{mr} = \left|<\psi_m\left|\hat{R}(\alpha,\beta,0)\right|r>\right|^2 \quad (4)$$

eigenvalues corresponding to the eigenfunctions ψ_m for the asymmetric rotor as given by Huntress,[6] and $\hat{R}$ gives the rotation matrix for the asymmetric rotor. All m, r, s, a, ··· indices run from −2 to +2.

* Bond lengths and angles were taken from the *X*-ray data for morphine,[8] naloxone,[9] and oxymorphone.[10] The geometry of nalorphine was derived by combining the data for morphine with those for naloxone. As confirmed by PCILO calculations of the conformational energy,[11] the geometry thus constructed proved to be a reasonable approximation.

† The possible conformations about N–C(17) and C(17)–C(18) were considered for both molecules (**3**) and (**4**). The moment of inertia tensors were found to be almost unaffected by the rotations of the allyl group.

Table 1. Carbon-13 n.m.r. chemical shifts (δ; Me_4Si) and corresponding carbon-13 n.m.r. spin–lattice relaxation times (T_1/s) for hydrogen-bearing carbon atoms in agonist–antagonist pairs [(1),(3); (2),(4)], as free bases, measured in the same medium [$(CD_3)_2SO$–$CDCl_3$, 1:1]

Compound	C(1)	C(2)	C(3)	C(4)	C(5)	C(6)	C(7)	C(8)	C(9)	C(10)	C(11)	C(12)	C(13)	C(14)	C(15)	C(16)	C(17)	C(18)	C(19)
(1)	118.5	116.5	138.4	146.15	91.3	66.2	133.3	128.2	58.1	20.2	125.4	130.9	42.9	40.5	35.4	46.0	42.7		
	0.56	0.48			0.70	0.54	0.63	0.64	0.58	0.45				0.58	0.31	0.30	0.74		
(2)	119.9	118.5	140.0	143.8	89.0	208.1	*a*	30.72	65.3	23.1	121.3	128.0	48.8	70.2	28.3	46.6	41.8		
	0.29	0.21			0.29			0.13	0.24	0.16					0.14	0.12	0.52		
(3)	119.4	117.1	138.7	145.8	91.3	66.3	133.3	128.3	56.4	21.1	125.8	131.0	43.4	40.6	35.5	44.5	58.1	135.8	117.3
	0.44	0.43			0.53	0.47	0.42	0.53	0.47	0.28				0.55	0.26	0.27	0.49	0.94	0.48
(4)	119.8	117.4	139.5	143.6	89.4	208.6	35.8	31.1	61.9	22.5	123.2	129.2	50.3	69.9	30.2	43.1	57.1	135.5	117.6
	0.43	0.43			0.47		0.23	0.20	0.39	0.25					0.21	0.23	0.45	0.82	0.36

[a] Signal collapsed (nucleus partially deuteriated).

Table 2. Motional parameters[a] for morphine (1), oxymorphone (2), nalorphine (3), and naloxone (4) as calculated from the best-fit analysis of T_1 data for an anisotropic rigid model[b] of overall reorientation with additional internal motion (% error of the fitting procedure is given).

Compound	% Error	$10^{10}\ D_1$	$10^{10}\ D_2$	$10^{10}\ D_3$	$10^{10}\ D_{av}$	α(°)	β(°)	γ(°)	$10^{10}\ D_{i(1)}$	$10^{10}\ D_{i(2)}$	$D_{i(1)}/D_{av}$	$D_{i(2)}/D_{av}$
(1)	7.7	2.021	0.145	0.738	0.968	10	80	50	8.00		8.26	
(2)	5.2	0.347	0.053	1.082	0.494	80	90	80	3.234		6.55	
(3)	8.2	0.608	1.301	0.281	0.730	10	30	10	1.351	1.219	1.85	1.67
(4)	2.2	0.417	0.866	0.650	0.645	20	60	10	0.552	0.104	0.86	0.16

[a] Calculated moments of inertia: (1) $I_A = 2\,015.59$, $I_B = 1\,591.41$, $I_C = 997.02$ a.m.u. Å^2; (2) $I_A = 1\,169.21$, $I_B = 1\,085.03$, $I_C = 2\,132.33$ a.m.u. Å^2; (3) $I_A = 2\,444.38$, $I_B = 1\,014.84$, $I_C = 2\,844.45$ a.m.u. Å^2; (4) $I_A = 2\,420.15$, $I_B = 1\,167.97$, $I_C = 2\,967.25$ a.m.u. Å^2. [b] D_1, D_2, D_3 are the diffusion rates along the principal axes of diffusion A', B', C', respectively; α, β, γ are the Euler angles; $D_{i(1)}$, $D_{i(2)}$ denote the internal diffusion rates around N–C(17) and C(17)–C(18), respectively; $D_{av} = (D_1 + D_2 + D_3)/3$.

The calculation procedure consisted of the initial fitting of the T_1 value for C(17) and, in successive steps, for C(18) and C(19). The method allowed the determination of two diffusion coefficients, $D_{i(1)}$ and $D_{i(2)}$, that reproduce best the experimental T_1 values of the carbon atoms of the allyl fragment in compounds (3) and (4). In the cases of compounds (1) and (2), a single parameter (D_i) obtains for the C(17) nucleus.

Results and Discussion

The carbon-13 n.m.r. chemical shifts of hydrogen-bearing nuclei are given in Table 1 together with the corresponding relaxation times. The δ values for (1) and (4) reproduce quite well those reported in the literature.*

The fitting procedure for the assumed anisotropic rigid model of molecular reorientation was initiated by using the whole set of relaxation data for each molecule. In all cases, results of computations showed that no minima of the function were attained and thus the fitting failed. The computational run was then repeated with exclusion from the input set of relaxation data the T_1 values of the carbon atoms involved in the possible non-rigid fragments, *i.e.* C(17), C(18), and C(19). This change produced good fits for the observed T_1 values of the remaining carbon atoms considered, which were used as input data. Although a definite single minimum occurs for (1), (2), and (3), in the case of (4) there are two local minima in the six-dimensional parameter space.† The dependence on the Eulerian angles of equation (2) was usually weak and therefore the Eulerian angles given in Table 2 have an estimated accuracy of the order of 10°. For this reason, it was unnecessary to reduce the scanning of the Euler angles below 10°.

At this stage, we can thus consider the foregoing results as providing evidence that: (i) the assumed model of overall molecular reorientation is valid and appropriate for interpreting T_1 data; (ii) the methyl as well as the allyl fragments correspond to the sites where the internal molecular motion is located. Sufficiently fast internal motions of these groups are present to make a contribution to the T_1 values of their carbon atoms.

The contribution of the internal motion to the relaxation of the carbon atoms of the methyl and allyl groups was evaluated by using, for the fitting procedure of the T_1 data, the set of diffusion coefficients (D_1, D_2, D_3) and Euler angles obtained from the fit accomplished for the model of anisotropic rigid overall tumbling.‡ The interpretation of T_1 data for (1)—(4), made in terms of overall anisotropic molecular reorientation with additional internal motion for C(17), C(18), and C(19) nuclei, gave the sets of motional parameters summarized in Table 2. To give an idea of the relative order of magnitude of the overall motions, Table 2 gives D_{av} values. These, while in general

* An inspection of the present data shows that on going from the pair (1),(3) to the 14-hydroxy compounds [(2),(4)] the C(9) resonances are shifted downfield (β effect) and the C(15) resonances upfield (γ effect). This provides support for previous views based only on the spectral data available for (1) and (4).[14] An interesting difference between the two pairs of analogous compounds is the large upfield shift (3.5 p.p.m.) for C(9) and C(16) resonances in the pair (2),(4) on passing from the *N*-methyl (2) to the *N*-allyl (4) derivative. The upfield shift for the same carbon atoms is smaller (1.5 p.p.m.) in compound (3) of the pair (1),(3). This shows that additional γ effects operate when the *N*-allyl group is present together with the 14-hydroxy group. Thus the combined effect of the associated structural and conformational change of ring C seems also important in determining the higher differential shifts for this pair. These observed differential shifts within each homologous pair cannot be rationalized in terms of changes of the geometry of the piperidine ring due to the *N*-alkyl substituent: this is excluded by *X*-ray structure determinations.[8–10] The trends found in the present systematic chemical shift data appear therefore in good agreement with the previously proposed interpretation[14] of some spectral features of compounds (1) and (4).

† The other possible local minimum found for (4) was excluded in view of the results of the subsequent calculation step which included internal motions. The use of the set of parameters given by this possible solution did not allow fitting of the T_1 data for the carbon atoms taking part in rotating fragments.

‡ As a check, we tried to find other possible α, β, γ, D_1, D_2, D_3, and related D_i values, close to the minimum, that could be compatible with all the experimental T_1 values. This search failed.

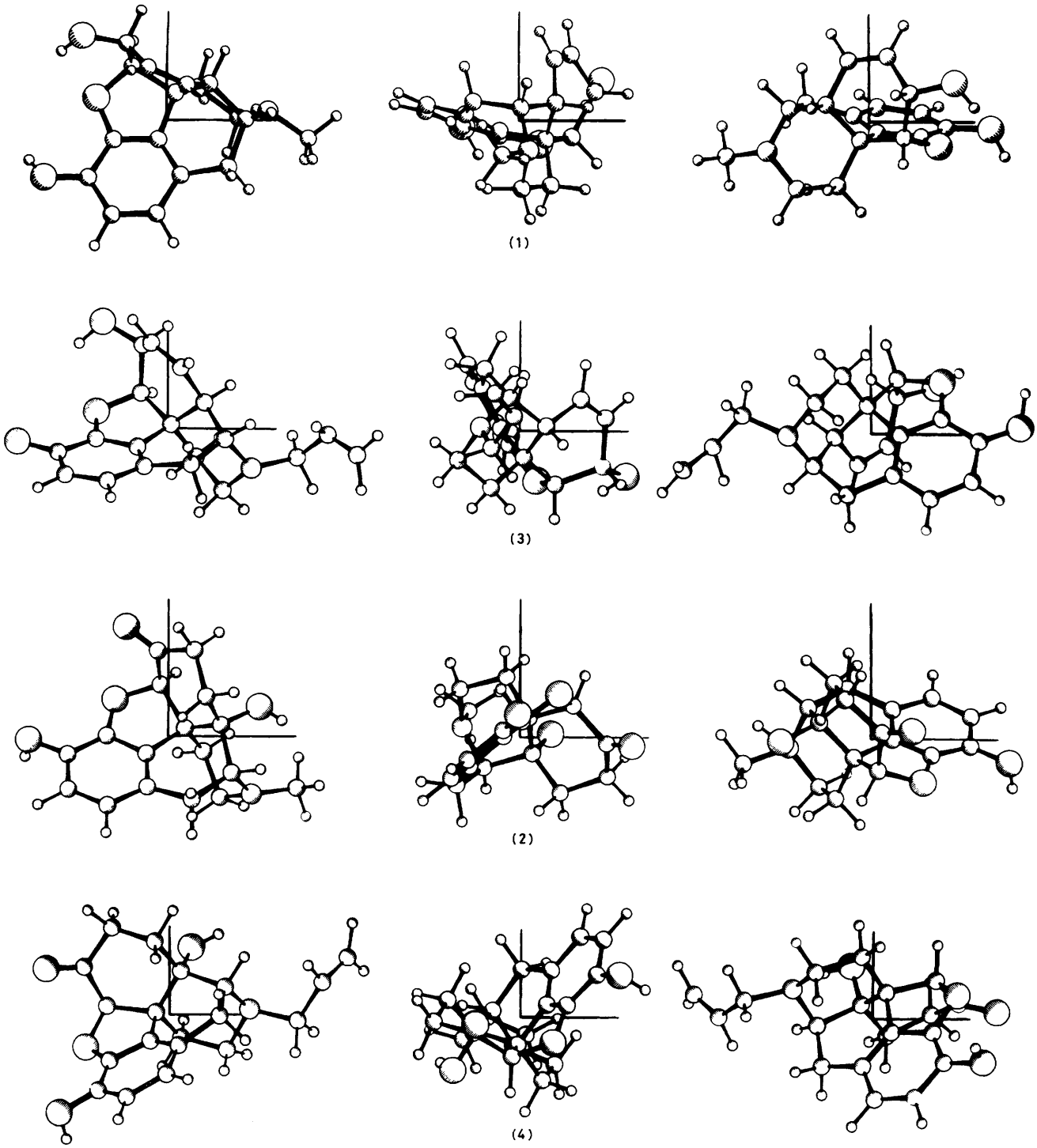

Figure. Molecular models of the pairs (**1**),(**3**) and (**2**),(**4**) viewed along the principal diffusion axes A', B', and C'. The computer-drawn (PLUTO program) projections are orthogonal to the planes $B'C'$, $A'C'$, and $A'B'$ in the order shown. The relative positions of the axes A', B', C', and as a consequence, of the Euler angles α, β, γ, are merely conventional: these parameters, in fact, may be defined at less than rotations of $\pm 90°$ or $\pm 180°$ in the plane of the paper, combined with reflections of $\pm 180°$ with respect to this plane.

reasonable and compatible with the molecular shapes and sizes, confirm that the adopted model works well. The sets of D and D_{av} data also show that it is the anisotropy which changes from compound to compound, thus giving rise to the separate characteristic diffusion rates about the principal axes of diffusion.

Values of D_{av} show that the diffusion rates for the pair (**1**),(**3**) are higher than for the pair (**2**),(**4**). A difference was expected, since the molecular backbone, that differs for the two pairs, is essentially the determining factor for the D values. The motional parameters for overall motion (D values and Euler angles) are summarized and compared, in a more concise

graphic form, in the Figure, which shows each molecular model viewed along each one of the three principal diffusion axes.*

With regard to the internal motions, the D_i values calculated for the methyl groups of (**1**) and (**2**) are diagnostic of an internal motion that is faster [especially for (**1**)] than the overall one. The values of D_i/D_{av} clearly indicate that the motion rates about C(17) and C(18) bonds in (**3**) are similar to that of the overall tumbling. In the case of (**4**) (naloxone), D_i values are smaller than the diffusion coefficients relative to the overall molecular motion ($D_i/D_{av} < 1$). This may appear odd and not in line with the assumed model. However, it must be considered, in principle, that internal motion will contribute to the observed T_1 values not only when the correlation time for the internal motion is similar or faster than that for overall motion, but also when the internal motion experiences a sufficiently large angular displacement.

These results, in general, provide evidence that the motional rate of the *N*-allyl group in compound (**4**) is considerably smaller than that of the same group in compound (**3**). This agrees well with results from theoretical quantum chemical studies,[15] since the findings indicate that rotation about the C(17)–C(18) and N–C(17) bonds, although of wide amplitude, is hindered in (**4**) by some intramolecular interaction that is not present in the allylic derivative of morphine (**3**).

The motional parameters and, in particular, the trend of some D_i and D_i/D_{av} values, might reasonably be correlated with the activity† of the compounds investigated. However, one should be aware that: (i) the significance of such a trend would be increased by further studies of molecular dynamics of additional samples of structurally similar pure antagonists and mixed agonist–antagonists; (ii) any hypothesis based on the present results will apply only if the relative order of magnitude of D_i values along the series, determined in $(CD_3)_2SO$–$CDCl_3$ solution, is retained in water (the medium that most closely mimics the conditions in the biophase). On the other hand, the effect of the solvent on the sequence of diffusion coefficients, and thus on the relative‡ internal molecular dynamics of molecules (**1**)—(**4**), may be assumed, at least qualitatively, to be minimal. It is unlikely that different solvents cause, for the same series of compounds, sufficiently large and opposite variations in energy barriers to bring about alterations in the relative rates of internal molecular motions. With this in mind, studies of motional features of narcotic analgesics and their antagonists would be of interest; further work along these lines appears of paramount importance.

* A common feature, which is observable among the projections along the diffusion axes, consists of a superimposable set of atoms which to some extent mimics dopamine. This feature may be easily recognized when all molecules are compared with each other with respect to the direction of their principal axes of diffusion after appropriate reflections and rotations in the plane of the drawings are made. However, before drawing any conclusion or proposing a model, it is essential to elucidate the basic problem of the possible relationships between rotational diffusion motion and interaction with the receptorial binding site. This constitutes a stimulating working hypothesis for future endeavours.

† The internal flexibility of the *N*-allyl group in the pure antagonist (**4**) is much lower than that of the same group in (**3**). This is consistent with the 'two-state receptor' hypothesis of Pert and Snyder;[16] the lowest motional rate of the *N*-allyl group in (**4**) could favour a more stable complex with the receptor in the antagonist conformation.

‡ It should be stressed that the sets of diffusion coefficients are to be interpreted in a relative fashion, to minimize the effects of solvent on the absolute values. Thus from experiments carried out in the same solvent for a series of structurally similar compounds one can compare the internal flexibility of a single compound with others of the series.

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