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Conformational Properties of Butaclamol and Isobutaclamol

Regularities in the Structures of Semirigid Neuroleptics

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SUMMARY

Conformational energy calculations have been performed on butaclamol and isobutaclamol using Allinger's MM2 (Molecular Mechanics II) program. *Cis* arrangements of rings D and E were found to be preferred by 1.4–1.9 kcal/mole for both compounds. Nevertheless, based on a molecular comparison with a number of semirigid neuroleptics, most notably loxapine and octoclothepin, it is suggested that *trans* arrangements are required for neuroleptic activity in the two compounds. However, *trans* conformer B of butaclamol, which was previously postulated as the biologically active form, was found to be 4.1 kcal/mole higher in energy, suggesting that it is less likely to play a significant pharmacological role. The biologically active forms are identified as *trans* conformer A for butaclamol and *trans* conformer B for isobutaclamol. Certain regularities in the structures of the semirigid neuroleptics are noted. It is also speculated that the *cis* conformers of protonated butaclamol may have unfavorable geometries for ion solvation, which would account for the anomalously low pK_a measured for the compound. A similar explanation would also account for a *trans* conformer being found in the crystal structures of the bromide salts of butaclamol and dexaclamol.

INTRODUCTION

The potent neuroleptic butaclamol (Fig. 1) has served as a model for a number for hypotheses on the molecular requirements for neuroleptic (dopamine antagonist) activity (1–5). In addition, various derivatives of it have been prepared and evaluated in an attempt to map out in detail the binding sites of the dopamine receptor responsible for its action (6, 7). This is because the compound is generally thought to have a well-defined multicyclic molecular geometry as well as strong stereoselectivity with dopamine antagonism only associated with the (+)-(3*S*, 4*aS*, 13*aS*)-enantiomer (1, 2). Despite its multicyclic structure, however, butaclamol does appear to have significant conformational flexibility. In addition to conformer A (Fig. 1a), which has been observed in the crystal structures of butaclamol and the closely related dexaclamol, the existence of a conformer B (Fig. 1b) has been postulated as having a somewhat better geometric correspondence to the structure of apomorphine (1, 2). The major difference between the two conformers is in the ethylene bridge between the two phenyl rings (A and C). Also, in addition to "transoid" arrangements of rings D and E (Fig. 1a and b), a "cisoid" arrangement (Fig. 1c and d) has been observed by X-ray crystallography for (+)-isobutaclamol (Fig. 2) that is geometrically and pharmacologically similar to butaclamol (7–9). Because of the importance of these model compounds, we have evaluated the relative stabilities of their possible conformers using theoretical molecular mechanics calculations.

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METHODS

Conformational energy calculations have been performed using the MM2 (Molecular Mechanics II) program and parameter set developed by Allinger and Yuh (10). The force constant and bond length of the C—C bonds in the phenyl rings were set to 8.0667 *md*/Å and 1.3937 Å as prescribed. This program has been shown to produce quantitatively correct thermodynamic results for hydrocarbons (11, 12). We have found the conformational and geometric results of the program and its predecessor to be in good agreement with those of X-ray crystallography despite the very different molecular environment of the two methods (13, 14)[1]. This includes being able to predict hitherto unobserved low-energy conformations that were subsequently observed using X-ray crystallography (13). Computed results for the compounds under study here should be relatively accurate, since they consist almost entirely of hydrocarbon with the few polar substituents being well separated in space. Full minimization of the energy with respect to all internal coordinates was performed. Special care was taken to ensure

[1] G. Hite, P. Salva, J. B. Anderson, M. Rapposch, M. Mangion, and M. Froimowitz, unpublished data.

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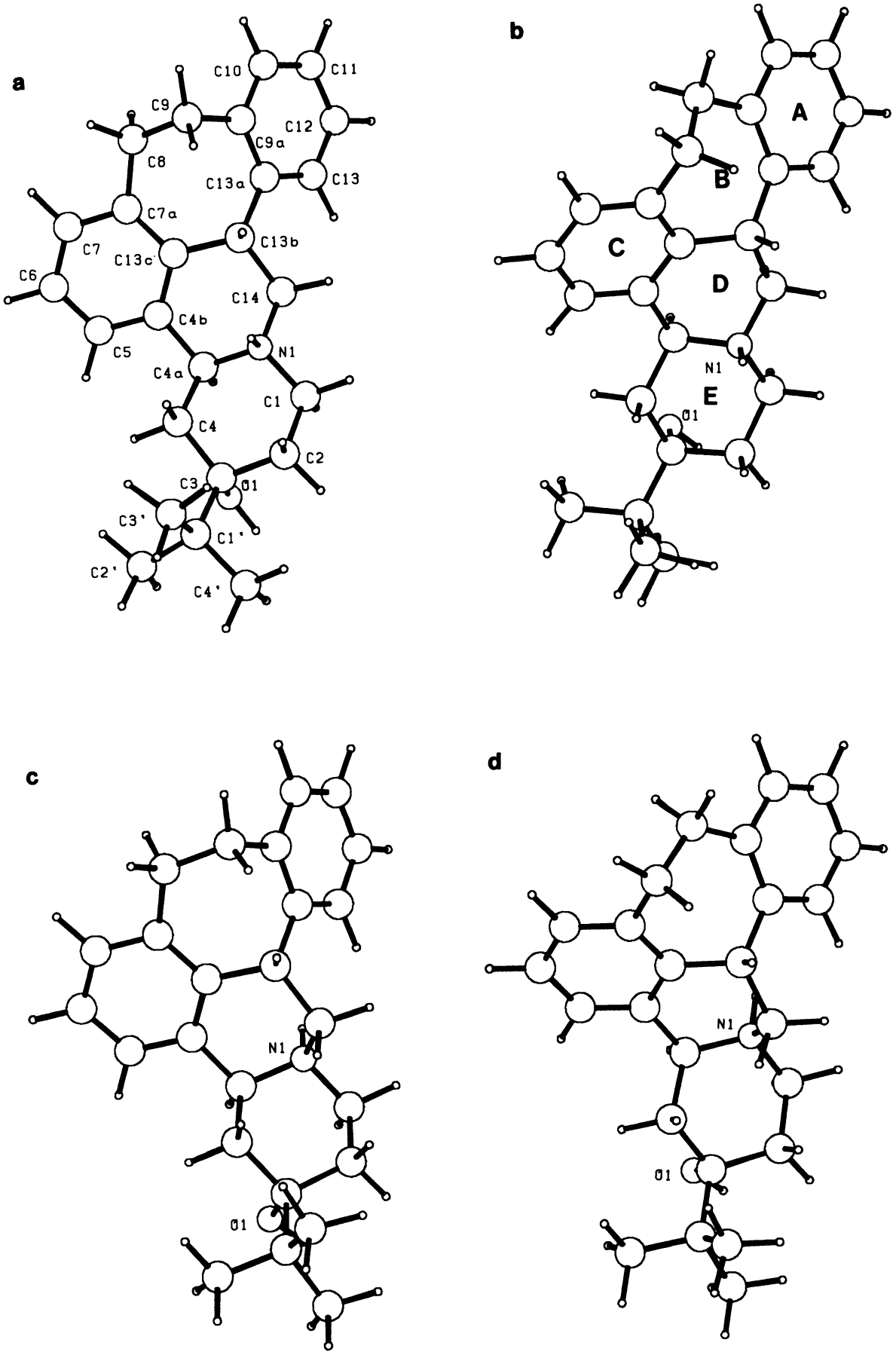

FIG. 1

that the minima found are the lowest for a particular conformation by confirming that different starting points reproducibly led to the same minimum.

The atomic numbering systems used in this work are the same as those used in the X-ray crystallographic studies (2, 9) in order to facilitate comparison with them. These are illustrated for butaclamol in Fig. 1a and for isobutaclamol in Fig. 2a. We have also adopted the nomenclature used previously for the different conformers. The dihedral angle convention is the same as that used previously (13, 14).

For butaclamol and isobutaclamol, combinations of conformers A and B with both *trans* and *cis* ring arrangements of rings D and E were examined. Calculations are reported for the protonated compounds, although it should be noted that butaclamol is predominantly unprotonated at physiological pH (7). Calculations performed on the conformers of unprotonated butaclamol were without any significant geometrical or energetic differences.

RESULTS

Detailed geometrical and energetic results of the calculations on butaclamol are presented in Table 1, with the four energy-minimized structures[2] found illustrated in Fig. 1. The two lowest-energy conformers, with about the same energy, were found to be conformers A and B, with *cis* arrangements of rings D and E. These were followed by the crystallographically observed *trans* conformer A, which was computed to be 1.4 kcal/mole higher in energy. *Trans* conformer B, which had been suggested as being responsible for the biological activity in butaclamol and related compounds, was computed to be a relatively unfavorable 4.1 kcal/mole higher in energy.

It is generally difficult to isolate the factors that contribute to energy differences between conformers in a molecule the size and complexity of butaclamol, since the higher energy of a particular conformer tends to be diffused over a large number of internal modes. However, the largest factors favoring the *cis* conformers are the bond-stretching and van der Waals' interactions. The apparent interpretation for this is that the *trans* conformers have somewhat less favorable steric interactions which cause some additional bond stretching. One internal coordinate that tends to parallel somewhat the energy differences is the C13a—C13b bond length, which stretches from 1.522 Å (0.19 kcal/mole) in *cis* conformer A to 1.553 Å (0.87 kcal/mole) for *trans* conformer B. The *trans* conformers, however, have somewhat more favorable torsional interactions.

The geometrical and energetic results of the calculations on isobutaclamol are presented in Table 2. The four minimized conformers[2] are illustrated in Fig. 2. As with butaclamol, a *cis* conformer is preferred. This is also the conformer found in the crystal state. This is followed by *trans* conformers A and B, which are 1.9 and 2.7 kcal/mole higher in energy. A second *cis* conformer is found to be relatively unfavorable, being 6.2 kcal/mole higher in energy.

[2] The energy-minimized coordinates of the conformers in this paper are available from M. F.

DISCUSSION

Although the two *cis* conformers are clearly preferred for butaclamol, they do not appear to be the biologically active forms, since their geometries are less consistent with those of other semirigid neuroleptics. A similar conclusion, based on a comparison with the dopamine agonist apomorphine, has been reached previously (1, 2). The nitrogen-phenyl center distances of a number of these compounds have been compiled in Table 3 (4, 5, 16–22). These range from 5.2 Å to 6.2 Å with the exception of the atypical clozapine. In clozapine, the phenyl substituent is on the ring opposite from those of loxapine and HUF-2046. However, clozapine has very weak dopamine antagonist potency as measured on neuroleptic receptor binding assays (23, 24). The range of intramolecular distances suggests that the essential molecular geometries for neuroleptic activity cannot be defined precisely. In addition, in our experience, the distance from the center of an atom to the plane of a ring tends to vary considerably, since it is very sensitive to slight tilts of the ring. The range of distances is not unreasonable, since both substrates and receptors to which they bind would be expected to have a certain amount of flexibility with which to accommodate each other. In the *cis* conformers of butaclamol, however, the nitrogen-phenyl distances are 4.3–4.5 Å for phenyl ring A and 3.7 Å for phenyl ring C (Table 1). These distances are shorter than the corresponding distances of other semirigid neuroleptics.

The more likely candidate for neuroleptic activity appears to be *trans* conformer A (Fig. 1a) that is 1.4 kcal/mole higher in energy than the *cis* conformers. For phenyl ring A, the nitrogen-phenyl center distance for this conformer is 5.2 Å with a nitrogen-phenyl plane distance of 0.5 Å, which now falls in the range of distances in Table 2. Conformer B, which has been proposed as the biologically active form of butaclamol, probably does not play a significant pharmacological role because it is 4.1 kcal/mole higher in energy. Although it is certainly possible for an energetically less favored conformer to bind to a receptor site because of the substantial quantity of energy released by the substrate-receptor interaction, it would appear that *trans* conformer A is much more likely to be the biologically active form than *trans* conformer B. Using the Boltzmann factor and assuming no significant entropic or solvation differences between conformers, the concentration of the former would be 10% of each of the *cis* conformers whereas that of the latter would only be 0.1%. Also, the very high receptor affinity of butaclamol (23, 24) makes it much less likely that *trans* conformer B is required for neuroleptic activity, since the substantial 4.1 kcal/mole penalty for assuming the conformation should adversely affect the stability of the substrate-receptor complex relative to other compounds.

Further evidence that *trans* conformers are the biologically significant ones for butaclamol may be obtained

FIG. 1. *The four energy-minimized conformations found for (+)-butaclamol*

The relative steric energies are (a) *trans* conformer A, 1.4 kcal/mole; (b) *trans* conformer B, 4.1 kcal/mole; (c) *cis* conformer A, 0.0 kcal/mole; and (d) *cis* conformer B, 0.0 kcal/mole. The major difference between conformers A and B is in the conformation of the ethylene bridge between phenyl rings A and C. The difference between *cis* and *trans* conformers is in the fusion of rings D and E. Note that all of these figures, except for 1c, and the remaining ones are drawn from the identical point of view with respect to phenyl ring A. Figure 1c has been rotated 10° to permit a better view of the amine hydrogen.

TABLE 1

Dihedral angles, intramolecular geometrical parameters, and steric energies for minimized conformations of butaclamol

The equivalent numbers for the crystal conformation of dexaclamol have been included to facilitate comparison.

	X-ray[a]	*Trans*		*Cis*	
		Conformer A	Conformer B	Conformer A	Conformer B
Ethylene bridge					
C8-C9-C9a-C10	107	105	−154	109	−178
C7a-C8-C9-C9a	62	77	−80	57	−58
C7-C7a-C8-C9	174	159	−104	179	−107
Phenethylamine					
C13-C13a-C13b-C14	16	11	−19	24	0
C13a-C13b-C14-N1	−169	176	−165	−90	−76
Ring B					
C9a-C9-C8-C7a	62	77	−80	−57	−58
C9-C8-C7a-C13c	−3	−20	75	−1	73
C8-C7a-C13c-C13b	−4	−4	0	0	−2
C7a-C13c-C13b-C13a	−51	−37	−56	−57	−70
C13c-C13b-C13a-C9a	70	64	34	73	55
C13b-C13a-C9a-C9	0	−4	1	0	−1
C13a-C9a-C9-C8	−75	−73	24	−70	2
Ring D					
C4b-C13c-C13b-C14	4	15	−1	−8	−20
C13c-C13b-C14-N1	−43	−52	−32	39	51
C13b-C14-N1-C4a	73	70	64	−64	−68
C14-N1-C4a-C4b	−62	−48	−59	54	49
N1-C4a-C4b-C13c	20	12	28	−23	−18
C4a-C4b-C13c-C13b	8	4	2	0	4
Ring E					
N1-C4a-C4-C3	−52	−60	−53	−53	−52
C4a-C4-C3-C2	55	52	52	49	49
C4-C3-C2-C1	−60	−48	−53	−50	−51
C3-C2-C1-N1	63	55	60	56	57
C2-C1-N1-C4a	−64	−63	−59	−56	−56
C1-N1-C4a-C4	55	63	54	54	53
Miscellaneous					
O1-C3-C4-C4a	−65	−63	−63	−66	−66
C1′-C3-C4-C4a	172	178	178	175	175
C2′-C1′-C3-C4	55	71	51	51	50
C3′-C1′-C3-C4	174	−170	170	171	169
C4′-C1′-C3-C4		−49	−70	−69	−71
N1-phenyl A center, Å	5.1	5.2	5.2	4.5	4.3
N1-phenyl A plane, Å	0.2	0.5	0.8	0.5	1.3
N1-phenyl C center, Å	3.7	3.8	3.7	3.7	3.7
N1-phenyl C plane, Å	0.8	0.4	0.8	0.5	0.3
Steric energy (kcal/mole)		31.1	33.8	29.7	29.7

[a] Computed from fractional coordinates in ref. 2.

from a comparison with the semirigid neuroleptic loxapine and octoclothepin (Figs. 3 and 4). The information that the two structures provide complement each other. In loxapine, there appear to be only two possible conformers: the one shown in Fig. 3 and its mirror image (16). This is a result of restricted rotation about the bond joining the tricyclic structure with the piperazine ring (16). There is ample evidence from X-ray crystallography, nuclear magnetic resonance, and PCILO (perturbation configuration interaction using localized orbitals) calculations that this bond has substantial double-bond character with high barriers to rotation in compounds of this class (16–19, 25, 26). Octoclothepin, on the other hand, does not have a double bond in the central ring to promote resonance, which results in two structural features. First, there are now two distinguishable mirror image compounds that have different neuroleptic activities, with the more active enantiomer shown in Fig. 4 (20, 27). Second, there should now be free rotation about the above bond, resulting in some uncertainty as to which conformer is responsible for neuroleptic activity, although it should be noted that the closely related oxyprothepine has a very similar conformation in its crystal state (21). With the use of the structures of both loxapine and octoclothepin, however, it is apparent that the conformers in Figs. 3 and 4 would be structurally equivalent. Also, it is important to note that ring A is the important one in loxapine and related compounds, since a chlorine substituent on it in the appropriate position greatly enhances their potencies (28), and also that the N-18 nitro-

gen is the crucial one for activity (29). All of the conformers of butaclamol (and isobutaclamol) have curvatures of the tricyclic structure which are similar to that of loxapine and octoclothepin shown in Figs. 3 and 4. There are then a number of similarities between these semirigid neuroleptics and the *trans* conformers of butaclamol, suggesting a correspondence. First, the amine hydrogen (or lone pair) in the compounds is pointing upward. There is evidence that the correct orientation of the amine hydrogen or lone pair is crucial for neuroleptic activity (5, 25) Second, the extra steric bulk of the structures (i.e., the remaining two rings of the tricyclic structure) is to the left. However, one significant difference between butaclamol and loxapine which has yet to be explained is that a chlorine substituent on either phenyl ring *decreases* potency (30, 31), whereas the opposite is true for loxapine and many other neuroleptics (28, 30). Of the other distinctly different semirigid neuroleptics in Table 2, none appears to be suitable for this kind of molecular comparison. In flutroline, it would appear that the amine hydrogen can point in either direction (4). In the pyrrolo[2,3-*g*]isoquinolines, the direction of the amine hydrogen has been found to be critical since, because of the flat nature of the molecules, this is the only major difference between the active and inactive enantiomers (5). However, it does not seem to be possible to characterize one side of the molecule as being more bulky than the other.

Isobutaclamol (Fig. 2) differs significantly from butaclamol in that there is an additional methylene group between phenyl ring A and the amine nitrogen, which increases the distance between the two. Nevertheless,

TABLE 2

Dihedral angles, intramolecular geometrical parameters, and steric energies of minimized conformers of isobutaclamol

The equivalent numbers for the crystal conformation have been included to facilitate comparison.

	X-ray[a]	*Trans*		*Cis*	
		Conformer B	Conformer A	Conformer B	Conformer A
Methylene bridge	128	124	103	125	106
C7a-C8-C8a-C9	−107	−107	−108	−108	−120
C7-C7a-C8-C8a					
Phenylpropylamine					
C13a-C13-C12a-C12	176	180	−118	177	−111
C14-C13a-C13-C12a	−173	179	103	−178	88
N1-C14-C13a-C13	−79	−148	169	−75	−161
Ring B					
C8a-C8-C7a-C13b	71	74	70	72	59
C8-C7a-C13b-C13a	−5	−3	2	−1	3
C7a-C13b-C13a-C13	−70	−66	−28	−71	−10
C13b-C13a-C13-C12a	63	54	−27	59	−48
C13a-C13-C12a-C8a	−4	0	63	−3	70
C13-C12a-C8a-C8	−4	0	−3	0	−1
C12a-C8a-C8-C7a	−49	−56	−75	−54	−73
Ring D					
C4b-C13b-C13a-C14	−18	−7	23	−16	37
C13b-C13a-C14-N1	45	−25	−56	47	−23
C13a-C14-N1-C4a	−64	60	68	−66	−25
C14-N1-C4a-C4b	51	−62	−44	49	58
N1-C4a-C4b-C13b	−24	31	11	−18	−44
C4a-C4b-C13b-C13a	8	3	−1	2	−4
Ring E					
N1-C4a-C4-C3	−56	−52	−60	−53	−56
C4a-C4-C3-C2	55	53	52	52	50
C4-C3-C2-C1	−55	−55	−49	−53	−49
C3-C2-C1-N1	57	60	55	57	53
C2-C1-N1-C4a	−56	−57	−62	−54	−55
C1-N1-C4a-C4	54	52	64	52	56
Miscellaneous					
O1-C3-C4-C4a	−44	−62	−62	−63	−65
C15-C3-C4-C4a	179	179	179	178	176
C16-C15-C3-C4	−177	170	−169	170	170
C17-C15-C3-C4	64	51	72	50	51
C18-C15-C3-C4	−56	−70	−49	−70	−70
N1-phenyl A center, Å	6.0	6.5	5.9	6.0	5.4
N1-phenyl A plane, Å	1.1	0.8	3.1	1.2	3.7
N1-phenyl C center, Å	3.7	3.7	3.8	3.8	3.6
N1-phenyl C plane, Å	0.5	0.8	0.2	0.4	1.1
Steric energy (kcal/mole)		28.8	29.6	26.9	33.2

[a] Computed from fractional coordinates in ref. 9.

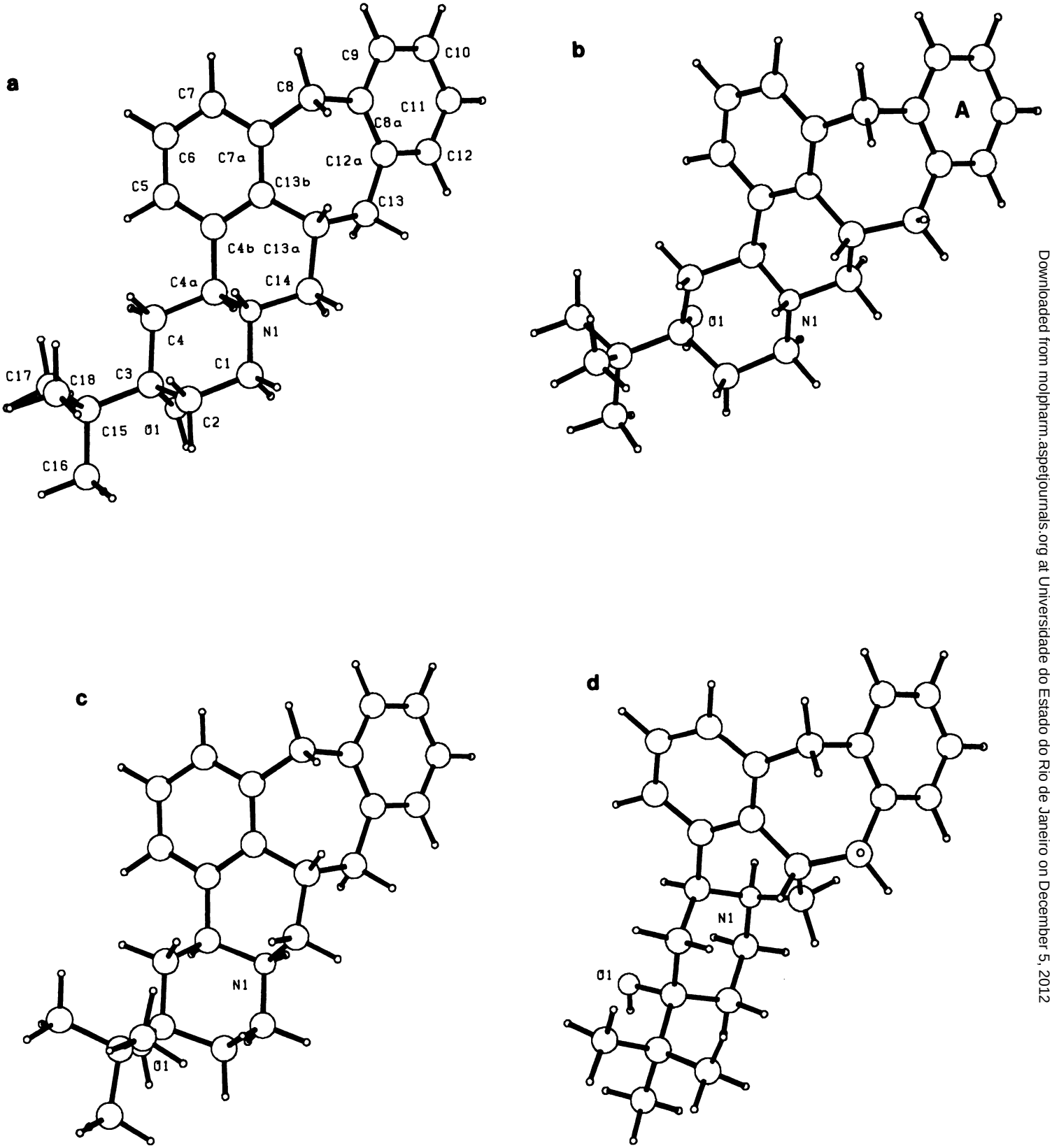

FIG. 2. *The four energy-minimized conformations found for (+)-isobutaclamol*

The relative steric energies are (a) *trans* conformer B, 1.9 kcal/mole; (b) *trans* conformer A, 2.7 kcal/mole; (c) *cis* conformer B, 0.0 kcal/mole; and (d) *cis* conformer A, 6.3 kcal/mole.

TABLE 3

Intramolecular geometrical distances and angles for a number of semirigid neuroleptics

For butaclamol and isobutaclamol, the data are for phenyl ring A. For the other compounds with two phenyls, the distances are measured from the one that contains the substituent. Where not available, the parameters were computed from the fractional coordinates in the indicated references (in parentheses).

	N-Phenyl center	*N*-Phenyl plane	Phenyl-phenyl angles
	Å	Å	
Butaclamol, *trans* conformation A	5.2	0.5	127°
Isobutaclamol, *trans* conformation B	6.5	0.8	104
Loxapine (16–18)	6.1–6.2	2.3–2.4	114–121
Clozapine (16, 19)	7.7–7.8	0.2–1.0	115–128
HUF-2046 (16)	5.9	2.7	118
Octoclothepin (20)	6.2	3.2	120
Oxyprothepine (21)	6.0	4.2	104
Flutroline (4, 22)	5.2	0.6	
Pyrrolo[2,3-*g*]isoquinoline (5)	5.9	0.1	

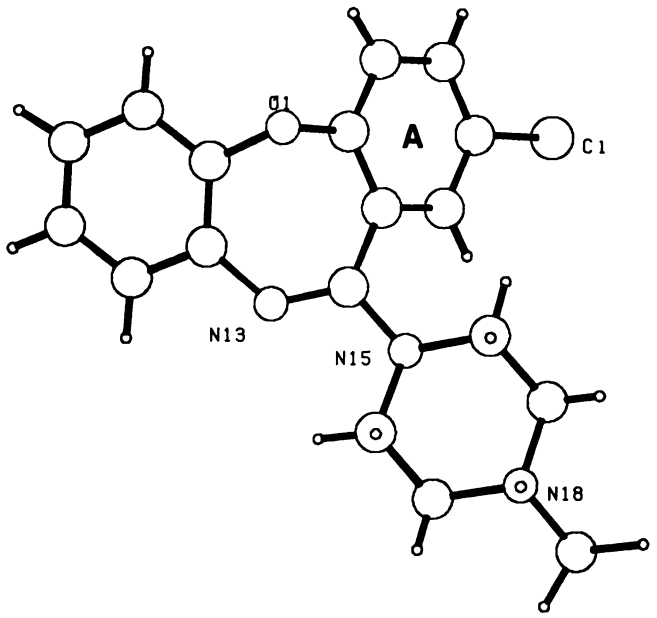

FIG. 3. *Molecular conformation found for the protonated form of loxapine using X-ray crystallography (18)*

since the two compounds share the same chirality (8, 9), it would seem likely that, if a *trans* conformer of butaclamol is crucial, it should also be crucial for isobutaclamol since this would also preserve the same orientation of the amine hydrogen (or lone pair). It would also appear to be likely that phenyl ring A in isobutaclamol would be the relevant one for the same reasons. The nitrogen-phenyl distance would then be 6.5 Å, which puts it somewhat further than that of the other compounds discussed above.

The clear preference for *cis* conformers in butaclamol may provide an explanation for the anomalously low pK_a (5.9) measured for the compound (7). As can be seen from Fig. 1c–d and as we have confirmed using a CPK space-filling model, the amine hydrogen in the protonated form would be in the narrow cleft formed by the two phenyl rings. Putting a positive charge into such a hydrophobic area would appear to be less than optimal as it may be difficult to solvate. Since solvation is a crucial step in the process, this may mean that the *cis* conformers cannot be easily protonated. Alternatively, it may be necessary for the compound to be converted to *trans* conformer A in order for protonation to occur. Either of these would result in a lowered pK_a. Unfavorable *cis* geometries may also account for the fact that *trans* conformer A is found in the crystal states of the hydrobromide salts of butaclamol and dexaclamol. Again, it would appear to be difficult to fit a relatively large bromide ion into a narrow hydrophobic cleft. In contrast, in isobutaclamol, where the extra methylene group between phenyl ring A and the amine group puts the latter further away from the cleft, a *cis* conformer is found in the crystal state of the hydrobromide salt.

COMPARISON WITH X-RAY STRUCTURES

In order to facilitate a detailed comparison between the computed geometries and those observed by X-ray crystallography, the dihedral angles that describe the crystal structures of dexaclamol and isobutaclamol have been included in Tables 1 and 2, respectively. The *cis* conformer B of isobutaclamol that is predicted to be the low-energy form by calculation is also found in the crystal state (9). The crystal conformation for dexaclamol and butaclamol is the *trans* conformer A (1, 2), whereas calculation suggests that *cis* conformers would be preferred. The energy of the former, however, is calculated to be only 1.4 kcal/mole higher. The difference between calculation and experiment may be due to crystal-packing forces, which are not considered in the calculations. As indicated above, the discrepancy between calculation and crystallography may be due to the unfavorability of putting a large bromide ion into the narrow cleft formed by the two phenyl rings. There is good agreement between the computed and experimental dihedral angles, particularly for isobutaclamol, whose crystal conformation is much more highly refined ($R = 0.033$ versus 0.090)

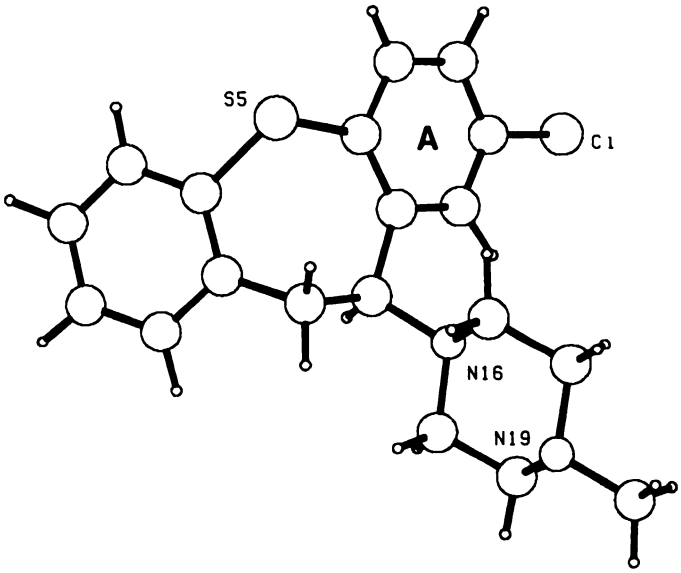

FIG. 4. *Molecular conformation found for (S)-(+)-octoclothepin, the more active enantiomer, by X-ray crystallography (20)*

In the protonated form, a proton on N19 would point upward.

(2, 9). The largest discrepancies are in the conformation of the *tert*-butyl group, which is rotated about 15°, and the oxygen, with the calculation predicting a more regular dihedral angle for it. Aside from these differences, the average discrepancy between the calculated and crystal dihedral angles is only 2.7° with a maximum difference of 6°. The good agreement with crystallography once again demonstrates the reliability of theoretical molecular mechanics using the MM2 program. The fact that predicted lowest-energy conformers, or those only slightly higher in energy, are found in the crystal state despite the very different molecular environments, strongly suggests that the conformational possibilities of the substrates are predominantly determined by the molecules themselves. Although the molecular environment of the receptor will undoubtedly influence the conformational distribution of the substrate molecule, only a conformer which already is favored is likely to be important.

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