

A quantitative investigation of the transannular amine–ketone ($N \cdots C=O$) interaction in medium-sized heterocycles

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The transannular $N \cdots C=O$ interaction in several medium-sized heterocycles has been investigated by force-field methods. Conformational searching has been performed at the molecular mechanics level using different methods and the conformers so generated have been reoptimized at RHF/6-31G(d). For selected conformers, $N \cdots C$ distances are reported, together with transannular bond orders and atomic charges. Good agreement with available X-ray crystallographic data is obtained for the transannular bond distance in cryptopine. Changes in the partial atomic charges derived from the electrostatic potential provide good support for the donor–acceptor model of transannular interactions. Partial charges derived with other methods do not give satisfactory results. Some force fields do not reproduce the transannular interaction very well. This is demonstrated and rationalized, and modifications are suggested and tested for these force fields with good results when comparing diagnostic geometric features with X-ray data.

Keywords: transannular interaction, ab initio calculations, force fields, medium-sized heterocycles

INTRODUCTION

Background

The transannular interaction of a basic nitrogen with a carbonyl carbon is well established in medium-sized heterocycles^{1–9}.

Color Plates for this article are on page 101–102.

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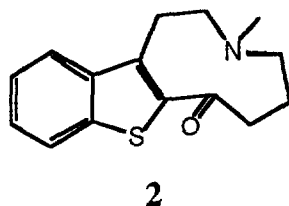
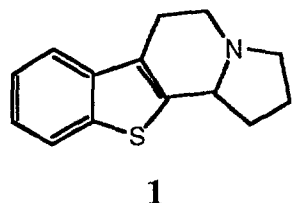
Paper submitted to the Electronic Conference of the Molecular Graphics and Modelling Society, October 1996.

Our interest in such systems has arisen from our desire to investigate their medicinal chemistry and evaluate their potential as pharmaceutical agents. In particular we are interested in ligands (antagonists and agonists) that bind selectively to specified subtypes of the dopaminergic and adrenergic receptors. For example, α_{1A} adrenoceptors in the human prostate are implicated in the bladder outlet obstruction seen in benign prostatic hyperplasia. Selective antagonists to this receptor subtype could lead to drugs for the treatment of benign prostatic hyperplasia¹⁰ that show fewer side effects than currently used nonselective drugs such as prazosin.

Selective α_2 antagonists are also of clinical interest as anti-depressants¹¹ and ligands of the dopaminergic D_4 receptor subtype are promising both in the diagnosis and treatment of schizophrenia¹².

The design principles involved in the achievement of such fine-tuning of ligand–receptor affinity are far from clear. In addition, there is considerable overlap between adrenergic activity and activity at other bioamine receptors, such as dopaminergic receptors. We have published a study on the development of pharmacophoric features to distinguish antagonists showing some selectivity for either the α_{1A} or the α_{1B} adrenergic receptors¹³.

To design selective ligands, structural information on the receptor subtypes, especially their binding sites, would be invaluable. There is, however, no X-ray crystal structure available for any bioamine receptor. One way of exploring possible design principles for the achievement of highly selective medicinal agents is by studying compounds that are structurally different from known drugs. Our work is concerned with the design, synthesis, and evaluation of novel medium-sized heterocyclic compounds that can act as ligands of bioamine receptors. In particular, it is intended to explore the effect on affinity in going from rigid, fused-ring compounds such as **1** to medium-ring compounds such as **2**:



Compound **1** has been synthesized and tested and is an α_2 antagonist (pK_i 8.15; rat cortex¹⁴). Compound **2** has a novel chemical structure and offers the potential for the development

of a new class of pharmaceuticals. The structural novelty combined with opportunities to modulate the conformational flexibility of medium-ring heterocycles provide a little-explored opportunity¹⁵ to elucidate receptor binding and recognition principles by small molecules. Compound **2** (the "lead molecule") additionally shows interesting conformational features: It is an example of a nine-membered nitrogen-containing heterocycle with torsional constraints. This "rigid group principle" to reduce the conformational complexity of medium-sized heterocycles has been employed before,¹⁵ but only a few examples of nine-membered rings have been studied. More importantly, the possibility of a strong intramolecular interac-

Table 1. Summary of observables for molecule 5 as obtained from conformations optimized at RHF/6-31G(d) level^a

Conformer, family (molecule)	Rel. tot. energy (kJ/mol)	d_1 (Å)	d_2 (Å)	α	Δ (Å)	Mulliken partial charges on:			Natural bond order partial charges on:		
						N	O	C	N	O	C
1, x (5)	12.51	2.72	1.192	97.2	0.058	-0.604	-0.544	0.577	-0.579	-0.644	0.701
2, x (5)	7.24	3.85	1.194	161.4	0.029	-0.571	-0.520	0.491	-0.578	-0.628	0.678
3, x (5)	0.00	2.91	1.195	104.4	0.007	-0.590	-0.544	0.532	-0.584	-0.643	0.683
4, x (5)	3.68	2.81	1.193	97.4	0.036	-0.592	-0.553	0.572	-0.581	-0.645	0.698
5, other (5)	6.07	3.76	1.196	108.7	0.002	-0.566	-0.543	0.507	-0.572	-0.635	0.667
7, x (5)	11.84	3.20	1.194	120.9	0.012	-0.577	-0.524	0.512	-0.576	-0.628	0.682
8, other (5)	13.10	4.63	1.194	148.9	0.03	-0.562	-0.522	0.499	-0.566	-0.626	0.674
14, other (5)	22.05	3.27	1.197	94.4	0.012	-0.574	-0.552	0.526	-0.590	-0.641	0.672
15, other (5)	23.43	3.86	1.193	105.3	0.001	-0.563	-0.526	0.525	-0.577	-0.624	0.676
16, x (5)	8.08	2.75	1.196	99.4	0.045	-0.606	-0.569	0.576	-0.589	-0.656	0.690
19, x (5)	14.52	2.72	1.194	100.7	0.078	-0.602	-0.556	0.570	+0.230	-0.652	0.701
20, other (5)	2.51	4.72	1.197	156.0	0.013	-0.563	-0.537	0.516	-0.562	-0.631	0.661
24, other (5)	10.38	4.04	1.194	95.8	0.001	-0.572	-0.530	0.513	-0.566	-0.645	0.672
25, x (5)	3.10	2.62	1.194	97.5	0.056	-0.622	-0.553	0.552	-0.581	-0.654	0.693
X-opt, x (5)	0.63	2.87	1.195	109.0	0.054	-0.589	-0.557	0.578	-0.585	-0.650	0.689
Crystal (3)		2.58	1.209	102.2	0.102						

Conformer, family (molecule)	Electrostatic partial charges on:			Mulliken bond orders		Natural bond orders	
	N	O	C	C-N	C-O	C-N	C-O
1, x (5)	-0.056	-0.586	0.756	0.007	1.853	0.048	2.212
2, x (5)	-0.260	-0.584	0.801	-0.001	1.845	0.007	2.217
3, x (5)	-0.241	-0.564	0.780	0.004	1.827	0.003	2.198
4, x (5)	-0.026	-0.596	0.705	0.006	1.826	0.037	2.192
5, other (5)	-0.518	-0.601	0.819	0.000	1.802	0.001	2.177
7, x (5)	-0.309	-0.573	0.823	0.002	1.852	0.003	2.221
8, other (5)	-0.602	-0.555	0.714	0.000	1.835	0.001	2.208
14, other (5)	-0.395	-0.545	0.652	0.001	1.798	0.002	2.174
15, other (5)	-0.593	-0.563	0.712	0.000	1.844	0.001	2.217
16, x (5)	+0.085	-0.589	0.653	0.007	1.795	0.041	2.161
19, x (5)	+0.015	-0.621	0.733	0.008	1.808	0.047	2.196
20, other (5)	-0.526	-0.572	0.702	0.000	1.794	0.001	2.177
24, other (5)	-0.586	-0.587	0.742	0.000	1.824	0.001	2.204
25, x (5)	-0.033	-0.578	0.744	0.010	1.822	0.053	2.187
X-opt, x (5)	-0.094	-0.598	0.787	0.006	1.810	0.032	2.178

^a Values obtained from the crystal structure of **3** are included for comparison.

Table 2. Summary of observables for molecule 6 as obtained from conformations optimized at RHF/6-31G(d) level^a

Molecule (conformer)	Rel. tot. energy (kJ/mol)	d ₁ (Å)	d ₂ (Å)	α	Δ (Å)	Mulliken partial charges on:		
						N	O	C
6 (2)	0.00	2.79	1.194	119.0	0.001	-0.594	-0.545	0.555
6 (3)	14.18	3.34	1.198	158.7	0.014	-0.580	-0.541	0.509
6 (4)	17.15	3.10	1.196	123.1	0.027	-0.614	-0.538	0.518
6 (X-opt)	9.71	2.76	1.193	112.8	0.058	-0.601	-0.532	0.547
4 (crystal)		1.99	1.258	110.2	0.214			

^a Values obtained from the crystal structure of **4** are included for comparison.

tion (the transannular interaction between the nitrogen and the carbonyl carbon) should modify the physical and chemical properties of the lead molecule (**2**).

The Transannular Interaction

Although the qualitative nature of the transannular interaction is well understood as a form of through-space homoconjugation,¹⁶ early attempts at modeling typical compounds with force field based and semiempirical molecular orbital-based methods^{6,8} and our work have shown (see below) that the N \cdots C=O interaction is not satisfactorily reproduced by these calculations. High-level *ab initio* molecular orbital-based calculations [RHF/6-31G(d)], as described below, have been successful in modeling the crystal conformations of compounds showing a moderate transannular interaction between a carbonyl carbon and a nitrogen atom.

It is, however, desirable for the purposes of ligand- and structure-based computer-aided drug design to be able to describe these molecules accurately, using molecular mechanics-based methods. This will enable us to use commercially available programs for pharmacophore development and for docking.

Aims

In this article we describe our calculations on molecules **3–6**, for which we expect or know a transannular interaction to be present. The investigation of the interaction was carried out at two levels of theory: molecular mechanics and *ab initio* molecular orbital theory [RHF/6-31G(d) level].

We also present simple modifications to a commercially available force field that enable us to describe the geometries resulting from the transannular interaction.

METHODS

Ab Initio Calculations

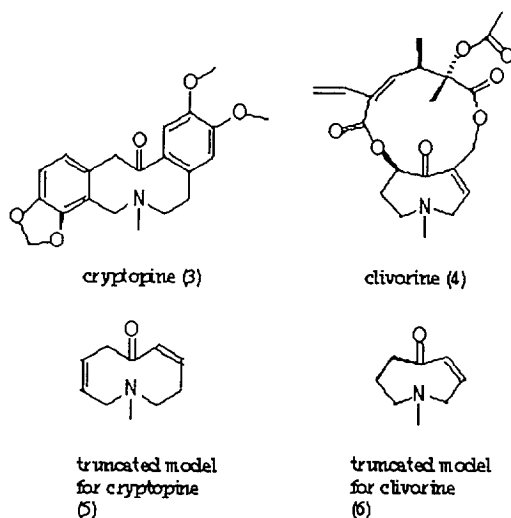
The *ab initio* optimizations were performed on a Fujitsu VP2200 supercomputer (Fujitsu Australia Ltd, North Ryde, N.S.W., Australia) using Gaussian 94 by Gaussian, Inc. (Pittsburgh, PA, U.S.A.). The input coordinates were obtained from conformational searching with molecular mechanics methods (noted below). Because of constraints on the usage of the supercomputer, only the truncated model compounds **5** and **6** were investigated at the RHF/6-31G(d) level. The optimized structures were then imported into Spartan by Wavefunction, Inc., Irvine CA, U.S.A. (on a Silicon Graphics (Gladesville, N.S.W., Australia) Indy workstation) for further calculation of properties such as the partial charges and for display. Bond orders and partial atomic charges were calculated via a Mulliken and a natural bond order analysis of the electron density^{17,18}. Partial charges were also derived from the electrostatic potential¹⁹.

Full details of these and our other *ab initio* calculations on the transannular effect can be found in Ref. 20.

Molecular Mechanics Calculations

Two types of calculations were performed here: (1) generation of conformers as input for *ab initio* calculations, and (2) molecular mechanics calculations with Molecular Simulations, Inc. (MSI) Milsons Point, N.S.W., Australia software.

Generation of conformers as input for *ab initio* calculations The truncated model compounds **5** and **6** were built within the Spartan software and conformational searching was performed using the "systematic" Goto and Osawa method²¹,



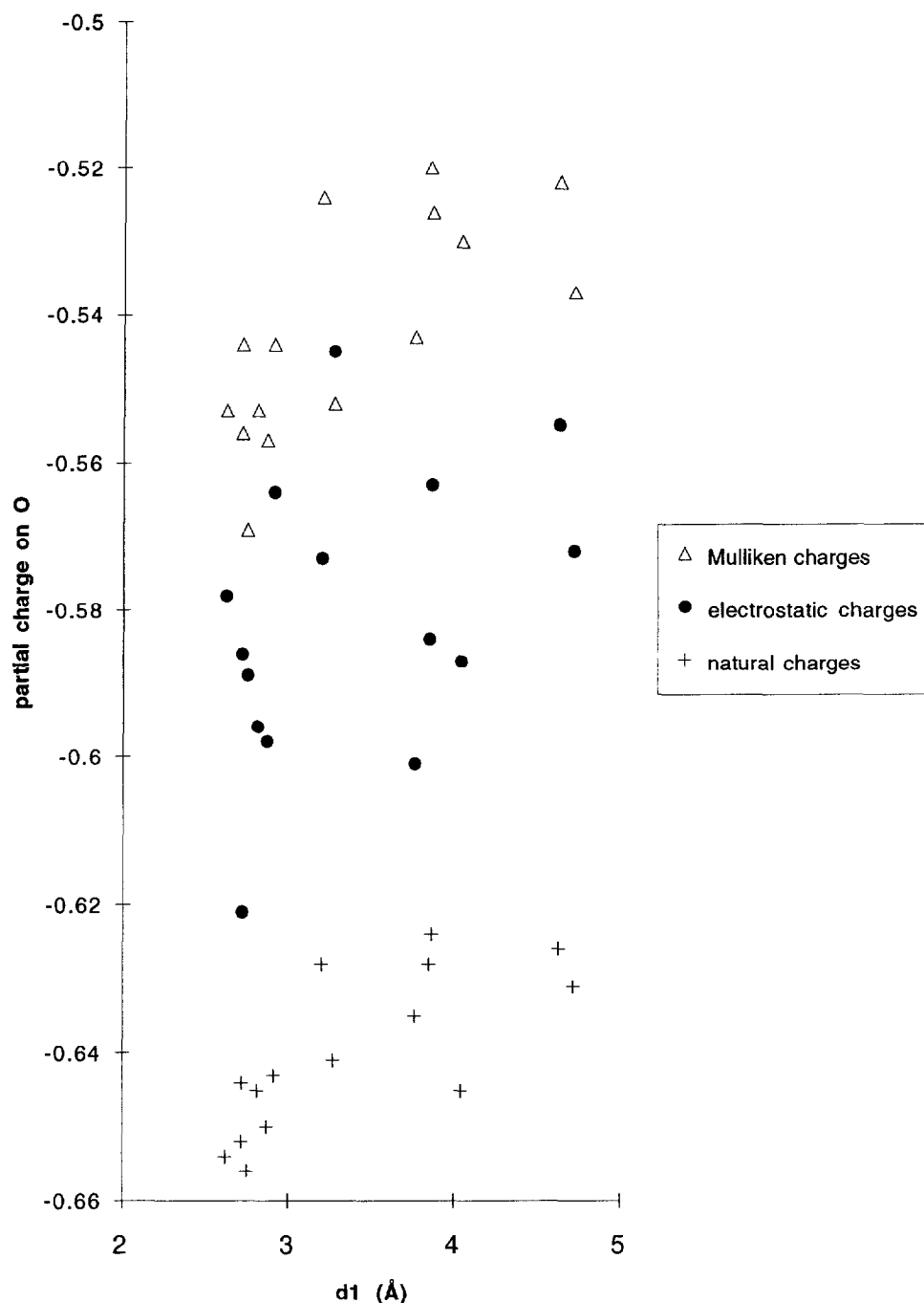


Figure 1. Partial charges on the carbonyl oxygen atom for selected conformations of molecule **5** versus transannular N...C separation (d_1). See text for methods of charge determination.

whereby individual ring atoms are alternatively “puckered up” and “puckered down.” The resulting structures were minimized using the Sybyl force field and duplicates discounted on geometric checking. Default settings were used; notably, the cut-offs for optimization were as follows: 0.001 Å for the displacements, 0.00001 kcal/mol for the energy, 0.0003 kcal/Å for the gradients, and 8.0 Å for the van der Waals interactions.

Molecular mechanics calculations with MSI software
These calculations were carried out on a Silicon Graphics Iris

Indigo workstation using MSI molecular modeling software, version 950, principally the InsightII and Discover modules for visualization and computation. The Discover module supports the proprietary CFF91, CVFF, and ESFF force fields as well as the AMBER force field.

The (fractional) X-ray coordinates of the test molecules cryptopine and clivorine (**3** and **4**) were typed from the original references^{22,23} into free format files. After definition of a format file these could be read by the software and atom types

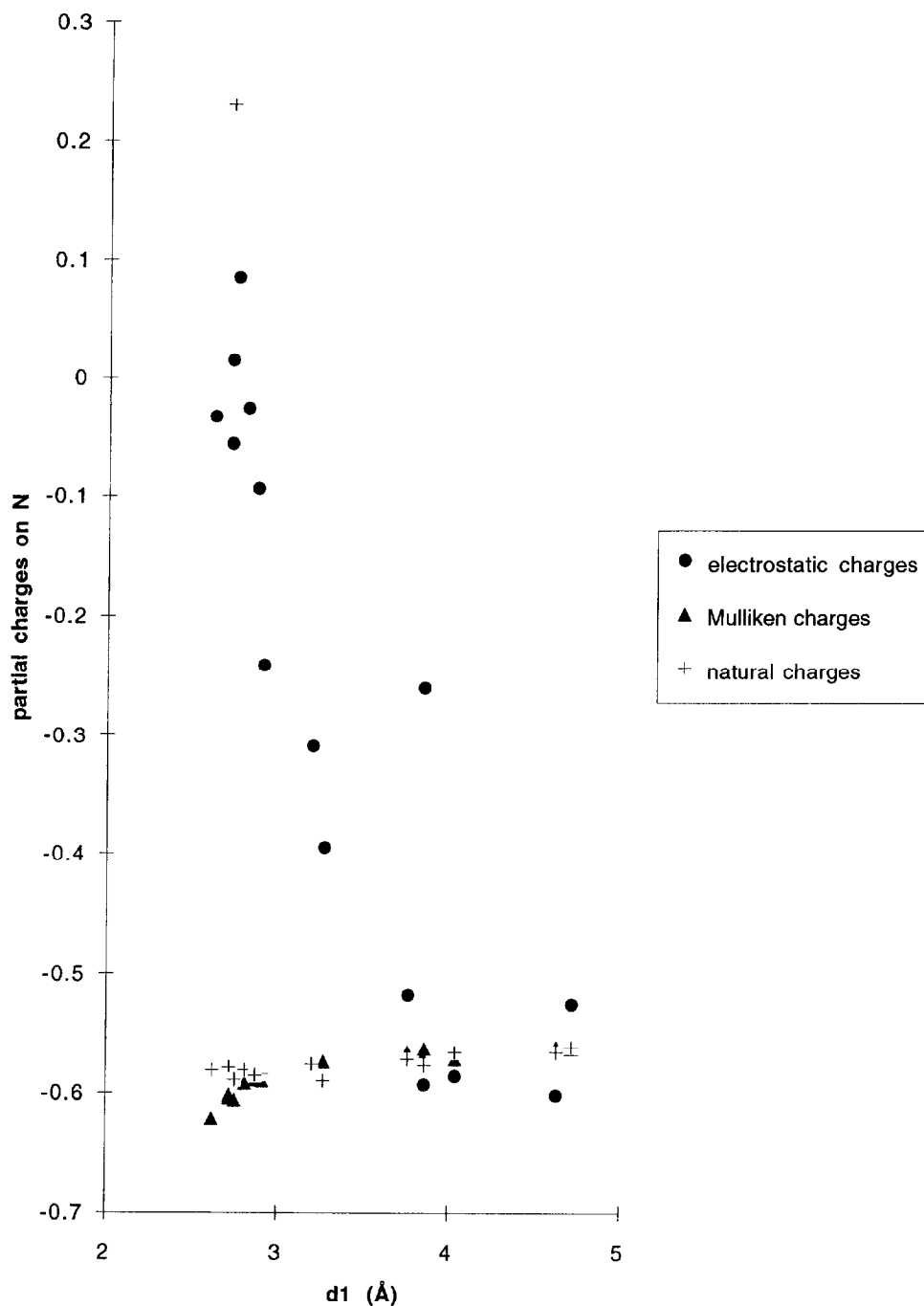


Figure 2. Partial charges on the nitrogen atom for selected conformations of molecule **5** versus transannular N...C separation (d_1). See text for methods of charge determination.

could be assigned. All molecules modeled were also sketched, converted into three-dimensional (3D) structures, and minimized to the closest local minimum using the MSI software.

All input structures were then subjected to molecular dynamics calculations in order to investigate the conformational space available to the molecules. Because the molecules all contain cyclic structures, no systematic searching methods were possible. The protocol was as described elsewhere²⁴. The CFF91 force field was the one selected for modification. The variations used entailed only the introduction of new atom

types and parameters associated with these, and the analytical expression used by the software for the force field and all other parameters were left untouched. The modifications were achieved by renaming the CFF91.frc text file and editing it using a UNIX text editor. The software then provides a utility for conversion of the edited text force field file newname.frc into a binary file newname.bin, which can then be selected for use by Discover. The other files associated with the force field (CFF91.rlb and CFF91_templates.dat) were just renamed, but not changed otherwise.

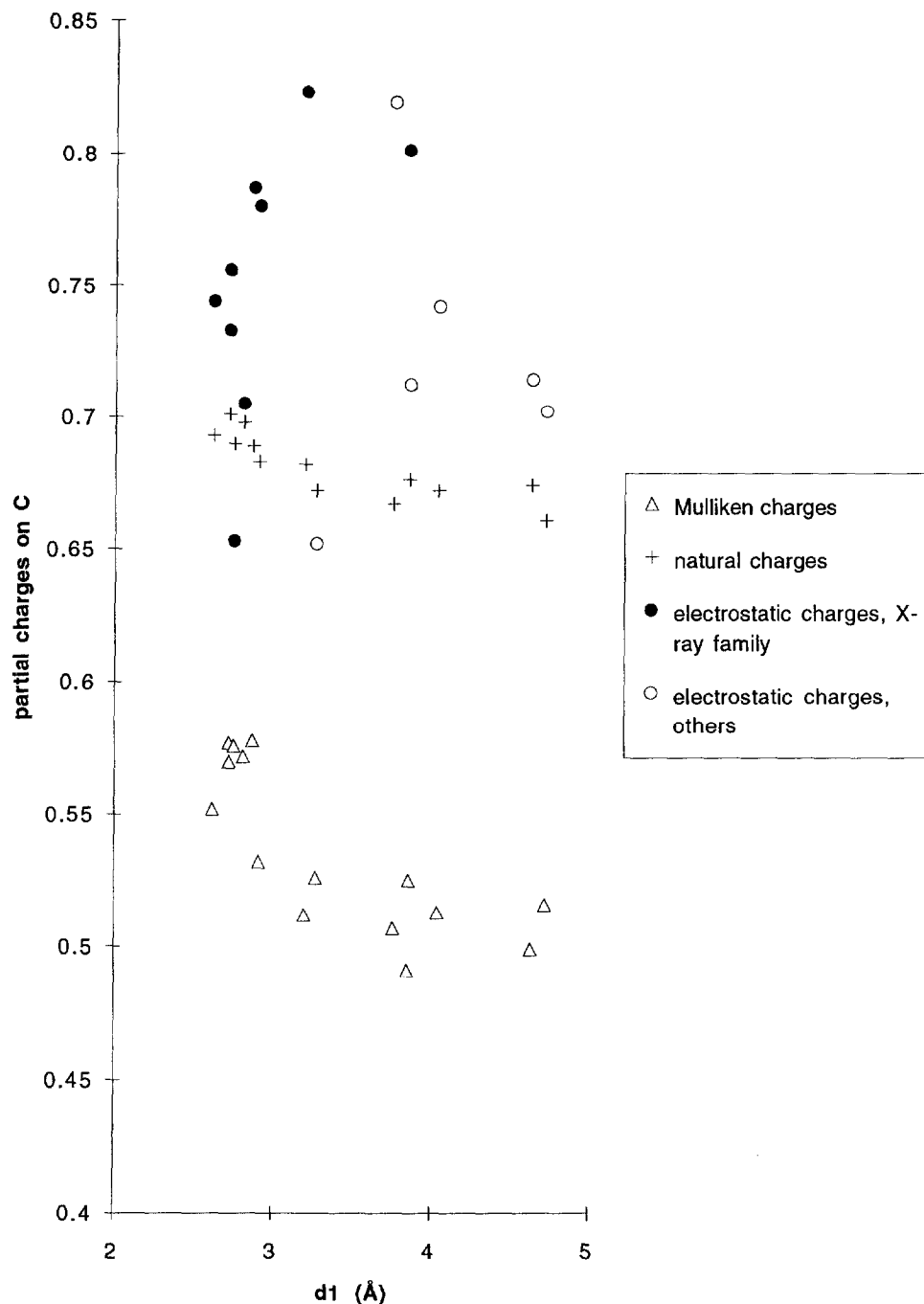


Figure 3. Partial charges on the carbonyl carbon atom for selected conformations of molecule **5** versus transannular $N \cdots C$ separation (d_1). See text for methods of charge determination.

Molecular dynamics calculations for conformational searching were performed in the edited force fields as described above.

RESULTS AND DISCUSSION

Ab Initio Calculations

The Osawa method for conformational searching for ring-containing compounds yielded *trans* isomers of the double bonds in the ring in the case of our truncated models **5** and **6**,

even though this possibility was supposedly suppressed. These *trans* isomers were discarded after visual inspection and 16 and 5 conformers were left for molecules **5** and **6**, respectively, within about 20 kJ/mol (with the Sybyl force field) with a range of transannular distances. However, reminimization at the RHF/6-31G(d) level led to a change in the spread of energy and distance values. Although conformers with short transannular distances were often low in energy, this was not consistently so. Although it would be desirable to carry out extensive conformational searching at more reliable levels of theory,

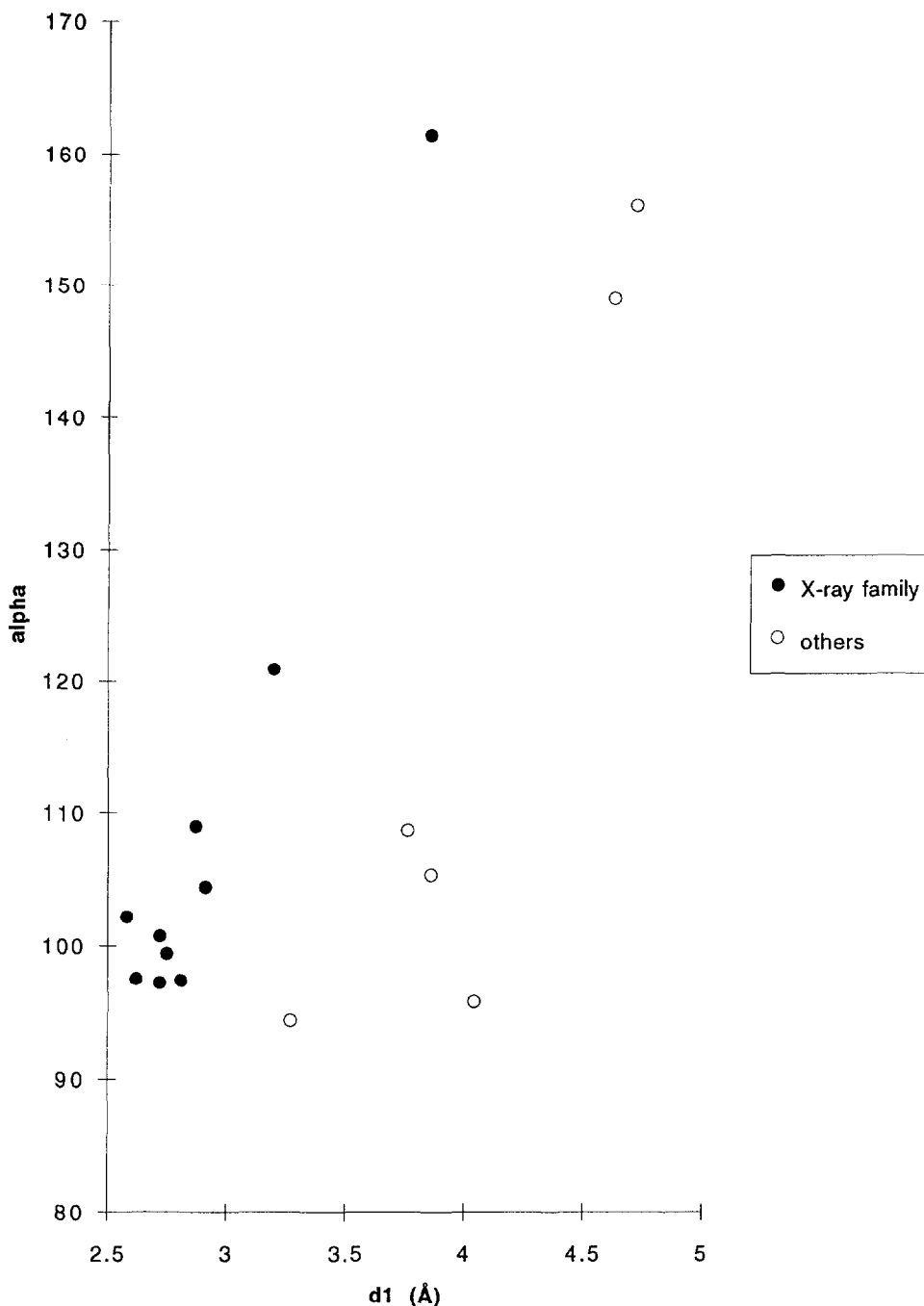


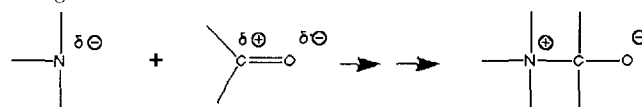
Figure 4. Transannular NCO angle (α) for selected conformations of molecule **5** versus transannular N...C separation (d_1), illustrating how the conformations can be subdivided into two families as shown in Color Plate 1. See text for details.

such an approach is clearly impractical at, say, the RHF/6-31G(d) level owing to time constraints. One indication for the completeness of conformational searching was obtained for molecules **5** and **6**. In both cases the X-ray structure coordinates for the parent (cryptopine [3] and clivorine [4], respectively) were imported into the Spartan program and truncated by deletion of atoms to molecules **5** and **6**. These structures were then also optimized at the RHF/6-31G(d) level and yielded conformers identical to ones already encountered (duplicates not included in Tables 1 and 2).

The results in Tables 1 and 2 show that there is reasonable

agreement in bond lengths between the calculated value and those obtained from X-ray crystallography, as long as the transannular interaction is not too strong. Clearly, even the RHF/6-31G(d) level of theory is not adequate to cope with such a strong effect as encountered in clivorine.

One way of depicting the transannular interaction is by a charge resonance as shown here^{2,3,7}:



Thus, the presence of a transannular interaction might be expected to lead to an increase in the charge on nitrogen (from a negative to a positive partial charge), a decrease in the partial charge on oxygen (more negative), and an increase in the transannular bond order, as well as a decrease in the planarity of the carbonyl carbon.

The transannular $N \cdots C$ separation (d_1 in Tables 1 and 2) is used as a measure of the transannular interaction in the following discussion.

The loss of planarity of the carbonyl carbon (Δ in Tables 1 and 2) on an increasing transannular interaction is the most straightforward effect and can be observed for both **5** and **6**.

The partial charges assigned to the three atoms involved in the transannular interaction vary considerably with the method used for their assignment. For the oxygen (molecule **5**), the natural bond order charges are most negative, followed by the electrostatic and then the Mulliken charges. In all cases, however, the oxygen becomes more negative as the transannular interaction becomes stronger (Figure 1).

For nitrogen, a different picture emerges (molecule **5**; see Figure 2). The Mulliken and natural bond order-derived charges are similar and vary only slightly with d_1 ; they actually become more negative, as the interaction becomes stronger, which would make the nitrogen the electron acceptor. Conformer **19** is the only one with a slight positive natural bond order charge on nitrogen, but there is no other indication why this particular conformer should be different from, say, the optimized crystal structure. The electrostatic charges on nitrogen behave in a completely different way and are in accord with both models to explain the transannular interaction; nitrogen donates electron density to the carbon atom.

For the carbonyl carbon the Mulliken and natural bond order charges show again different absolute values, but the same trend, which, if correct, would make the carbonyl carbon atom an electron donor in the transannular interaction (Figure 3). The electrostatic charges on the carbon again show a totally different trend. They can be explained, however, only if one first divides the conformers into two families as is rationalized here.

The transannular interaction between a carbonyl carbon and a nitrogen atom has been used in the past^{5,9} as a model for the nucleophilic addition of an amine to a carbonyl group. Crystal structures of different compounds with different transannular $N \cdots C$ distances have been used by Bürgi et al. to map the reaction coordinate. We present the same approach here, using different conformers of the one molecule (**5**). One proviso, however, must be made, and this is illustrated in Figure 4. If one plots the $N \cdots C$ separation (as a measure for the interaction) versus the approach angle α (NCO angle) two distinct families of conformers are observed (Figure 4).

Only the X-ray family can be used to map the reaction coordinate, because only it has the lone pair on the nitrogen pointing toward the carbonyl carbon (Color Plate 1b). For the other conformations, the nitrogen lone pair points away from the carbon (Color Plate 1a).

The behavior of the electrostatic charges (Figure 3) on the carbon can now be rationalized as follows. For both families of conformers the electrostatic charge on carbon decreases with increasing transannular interaction, consistent with carbon accepting electron density from the nitrogen. The two different families of conformations behave differently in other ways, too. There is essentially no correlation between d_1 and the C–O

bond order for the “other” family, whereas for the X-ray family the bond order drops slightly with an increasing transannular interaction.

The C–N bond order increases smoothly with increasing interaction for the X-ray family and stays virtually constant at a low level for the other conformations.

If we consider the total (relative) energy, then the transannular interaction plays only a small part. For all the conformers with d_1 greater than 3 Å, there is a weak correlation and the energy rises slowly as the $N \cdots C$ separation decreases. Below 3 Å (for **5**) the energy rises quite steeply as the two atoms approach, indicating that any energy gain by the interaction is far outweighed by unfavorable van der Waals interactions. Interestingly, this trend is reversed for the clivorine model **6**. Here the relative energies fall smoothly as the transannular separation decreases. How strong is the transannular effect? It appears from our calculations that it is not strong at all, and in some cases it is even calculated to be repulsive. However, it must be realized that our calculations are strictly relevant to isolated gas-phase molecules only and it is quite possible that small repulsive interactions could be overcome by solvation and crystal packing effects. Our calculations also do not take into account any electron correlation effects and this may limit their application to systems (such as cryptopine [**3**]) with limited transannular interactions only. To study a molecule like clivorine (**4**; $d_1 = 1.99$ Å), a higher level of accuracy will have to be employed again.

Molecular Mechanics Calculations

We have submitted the results obtained for the test molecules cryptopine and clivorine (**3** and **4**) using different force fields, as compared to the crystal structures²⁴.

In summary, none of the proprietary force fields in the MSI software can model molecules showing a transannular interaction between a nitrogen and a carbonyl carbon. The Sybyl force field by Tripos, Inc. as supported in the Spartan software, can, however, account for a moderate degree of interaction by allowing a closer approach of the two atoms involved. The same seems to be true to a lesser extent for the AMBER force field as supported in the MSI software, but this force field is severely lacking in parameters, e.g., for an isolated, as opposed to an aromatic, sp^2 carbon atom.

For drug design and development it is important to be able to use force field-based methods for reasons of computational cost, consistency and transferability (whole suites of integrated products are available from different suppliers), ease of manipulation (especially manipulation such as superimposition of families of conformers) and visualization of structures, coupled with the 3D pattern recognition modules Apex 3D and Catalyst, which are available within the MSI suite of products. For this reason it was decided to modify one of the proprietary MSI force fields to achieve a more accurate description of the model systems. The CFF91 force field was chosen, because it gives the best results before modification. It should be stressed that no attempt has been made to derive new parameters in a systematic way; only a “quick fix” solution to better reproduce experimental geometries was sought²⁴.

Two different approaches to the modification of the force field have been explored and are fully described elsewhere²⁴:

Approach 1. *The transannular interaction between a carbonyl carbon and a nitrogen is treated as a weak bond:* The

strength of this new carbon–nitrogen bond was set to 5% of that of a normal single bond between a carbonyl carbon and a nitrogen atom. The C=O carbonyl bond strength was accordingly reduced to 95% of its normal value. The bond length for the transannular bond was set to 2.581 Å and the carbonyl bond length to 1.209 Å, which are the values found for cryptopine in the crystal. All torsion parameters involving the C_{new}–N_{new} bond were set to zero. Results from the molecular dynamics treatment of both model molecules with this modified force field, called newCFF91, are summarized in another report²⁴. In general, it can be said that the conformational flexibility of the medium-sized heterocycles is severely curtailed by the introduction of the additional bond across the ring. The presence or absence of a force restraining the carbonyl carbon to planarity is not significant in this modified force field.

Color Plate 2a further illustrates the performance of this modified force field for the model compounds. The crystal structures for cryptopine (i) and clivorine (ii) are shown superimposed (using all heavy atoms in the medium-sized rings) on to the calculated structures and good agreement is observed. The results for clivorine are better than with any of the unmodified force fields.

Approach 2. *The transannular interaction is treated in a manner similar to the treatment of hydrogen bonds in this force field:* The nonbonded parameters for both the carbonyl carbon and the nitrogen involved in a transannular interaction were scaled down in this approach, but all other parameters for these atom types were used unchanged.

For clivorine and (to a lesser extent) for cryptopine, this force field modification does indeed allow the two atoms involved in the transannular interaction to approach closely and can thus model the X-ray structure quite well with very little increase in the total energy. It is also observed that a number of other low-energy conformations are accessible to the molecule. This is expected and has also been observed with our *ab initio* calculations (see above).

The effect of removing the out-of-plane readjustment force completely for the carbonyl carbon has also been investigated. This modification (denoted with an asterisk) does seem to improve the fit of both model systems to the X-ray structure.

Color Plate 2b illustrates the performance of this modified force field for cryptopine (i; the cryptopine* structure does not bear any resemblance to the crystal structure) and clivorine* (ii). The agreement is not good for cryptopine, possibly owing to selection of a “wrong” conformation out of the number of possible conformations. For clivorine, there is excellent agreement.

The target molecule **2** can now easily be modeled in both the modified force fields and compared to ADT16 (**1**), as is demonstrated in Color Plate 2c. ADT16 has been modeled in the unmodified CFF91 force field and the target molecule in newCFF91 (i) and nonCFF91 (ii).

For each run, the minimum energy conformation has been selected and the two compounds have been superimposed using all heavy atoms they have in common. As discussed for cryptopine above, the nonCFF91 force field allows a variety of conformations, and it is not immediately obvious which would be the “best” one. The newCFF91 force field, however, shows good agreement.

From this study we would therefore predict compound **2** to be able to mimic compound **1** and therefore show affinity for the α_2 adrenergic receptor subtype. Compound **2** is currently being synthesized in our laboratory and its affinity will then be tested *in vitro*.

ACKNOWLEDGMENTS

The authors thank the Australian Research Council (ARC) for financial support of this project, and the Australian Institute of Nuclear Science and Engineering (AINSE) and the Australian Nuclear Science and Technology Organisation (ANSTO) for a grant of supercomputer time on the VP2200/10. S.T. thanks the Institute for Molecular Recognition at the University of Wollongong for the grant of a summer vacation scholarship.

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