# Theoretical Investigations of Methanesulphonamide as a Hydroxy Group Equivalent in Drugs. Examples from Possible β-Adrenergic Agents and Analysis of Computational Methods

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Quantum chemical methods were used to analyse various physical chemical properties and interaction characteristics of methanesulphonamide. Comparison of β-methylsulphonylaminophenethylamine with its hydroxy analogue and certain structural fragments was used to examine the structure–activity relationships of arylhydroxyethylamines. The general role of methanesulphonamide as a hydroxy replacement was examined. In particular, based on the results of the calculations presented here, the differences in proton affinities, proton-donating abilities, or conformational properties do not account for the differences in activities of these compounds. Critical evaluation was made of several quantum chemical methods used in the study of these and other possible drugs, including the semiempirical MNDO and MINDO/3 methods and the *ab initio* Hartree–Fock method with the STO-3G, 3-21G, and 3-21G(*) basis sets.

The search for pharmacophoric equivalents to replace various functional groups is prevalent in the design of new drugs by medicinal chemists. The success of this approach lies in the ability of the replacement group to mimic the physical chemical properties and reaction characteristics of the original substituent. These features can often be studied directly by quantum chemical methods. In this work we use and analyse such methods as applied to the study of methanesulphonamide (MS).

MS has been used successfully to replace hydroxy groups in a number of different compounds. For example, MS has been used to replace the phenolic OH in the β-adrenergic agonist *N*-isopropyloctopamine to give the partial agonist sotalol [1] and in the dopamine agonist epinine [2] to provide analogues which retain dopamine agonist activity. It has also been used as a replacement group for aliphatic OH in the side-chains of prostaglandins.[3] In contrast, our studies [4] employing β-methylsulphonylaminophenethylamines and β-methylsulphonylaminoaryloxypropylamines showed that the MS group was not biologically equivalent to the aliphatic OH group of the parent compounds because they were found to be inactive as β-adrenergic agonists or antagonists in several $\beta_1$- and $\beta_2$-adrenergic screens. Non-receptor-mediated membrane depression activity was retained by these compounds. In our previous work,[4] we presented some preliminary findings from computational chemical methods used to explore possible explanations for the inactivity of these compounds as β-adrenergic agents. These studies are extended herein to further examine the structure–activity relationships of the β-substituent of β-adrenergic agents and to better understand the properties of MS.

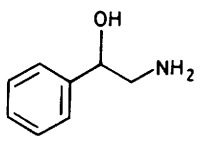
The MS group is an example of a biologically interesting molecule which contains a second-row atom. The reliability of different quantum chemical procedures used to conduct studies involving second-row atoms still needs to be firmly established. This is especially important in *ab initio* quantum chemical studies where more elaborate methods become extremely costly, whereas results from computationally less intensive techniques may be less reliable when second-row atoms are present.[5] Various quantum chemical methods, therefore, are compared in this work.

## Methods

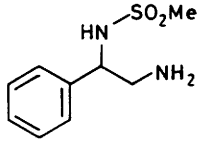
Semiempirical quantum chemical calculations were performed using the MNDO [6] and MINDO/3 [7] methods of Dewar *et al.*, as implemented in a version of MOPAC [8] modified by J. McKelvey.[9] Structures were obtained by full optimization of all geometrical parameters. *Ab initio* Hartree–Fock calculations were performed using the GAUSSIAN 82 [10] system of programs with the STO-3G,[11] 3-21G,[12] and 3-21G(*)[13] basis sets. The structures used for the *ab initio* schemes were, as indicated in the text, either fully optimized for the given scheme or from fully optimized results of semiempirical or other *ab initio* schemes. The notation employed to designate the structure used for a given calculation is that of the Pople group,[14] *i.e.* a calculation with method A using the structure obtained from method B is designated as A//B.

## Results and Discussion

*Proton Affinities.*—One property often involved in arguments regarding the relative ability of one functional group to replace another is their ability to act as an electron-rich group in a proton-accepting role. In our case, we were interested in why replacement of the β-hydroxy group in compounds such as (1) by an MS group to form related structures such as (2)




(1)




(2)

eliminated the activity of β-adrenergic receptors.[4] It was suggested that in (1), at physiological pH, the side-chain amine is protonated and is likely to be the primary element of recognition when binding to an electron-rich region in the receptor (see region I of Figure 1).

If the MS group in (2) also showed a significant propensity towards protonation, then it might compete with the side-chain amine for that interaction. Thus, (2) could be

inactive because either (i) this new alignment brings some other portion of the molecule to a region where it cannot undergo some secondary interaction needed for binding to the receptor (see region II of Figure 1) or (ii) the protonated MS group is not equivalent to the protonated amine in its interaction with I. The exploration of these possible explanations requires a reliable and efficient method for measuring the proton affinity of the MS group relative to the amine group. In this work, we model these two portions of the molecule with MS and $NH_3$, respectively. To make the comparison complete, we also have included $H_2O$ as a model for the OH group.

The proton affinities for MS, $NH_3$, and $H_2O$ are presented in Table 1. For each of the methods used, the values were calculated using fully optimized structures. The STO-3G results show that the MS has the highest proton affinity (293.0 kcal $mol^{-1}$), *i.e.* higher than $NH_3$ (259.4 kcal $mol^{-1}$). These orders are reversed in the 3-21G and 3-21G(*) calculations. We note that the difference in the $H_2O$ and $NH_3$ proton affinities using the 3-21G(*) basis set parallels that of the experimental values (Table 1).

The structures of the neutral MS are summarized in Figure 2. The most pronounced differences among the results with different basis sets are the sulphur–oxygen bond length and the angles of the nitrogen atom. Interestingly, for the *ab initio* calculations, only the results with the 3-21G(*) basis set predict a planar nitrogen. The semiempirical MINDO/3 results also predict a planar nitrogen, whereas the MNDO results do not. Thus, for MS, MINDO/3 appears to be the more reliable semiempirical method when compared with 3-21G(*).

The observed sensitivity of the *ab initio* calculations to the basis set used, particularly when second-row atoms are present, is not unusual.[14] These results are consistent with the findings of others that the STO-3G basis set tends to give less accurate structures for compounds containing second-row atoms than split-valence basis sets.[14]

*MS as a Proton Donor.*—An alternative mechanism by which MS could serve as a replacement for other functional groups such as OH involves proton donation. For example, in our previous work[4] we considered the relative ability of the amino proton on MS and a hydroxy proton to be donated. In that model, the OH group was explored as a possible proton donor in some secondary interaction which takes place on binding of the β-hydroxyphenethylamines to β-adrenergic receptors (see Figure 1, Region III). If such an interaction were required for binding at these sites, the inactivity of the compounds in which the MS group replaces the OH group[4] could be explained on the basis of the relative proton-donating ability of MS; *i.e.*, is MS a poor proton donor when compared with OH? This possi-

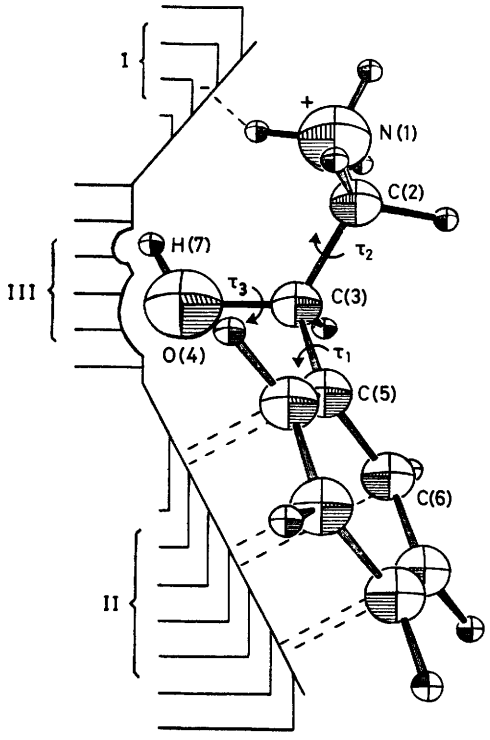



**Figure 1.** Possible regions of interaction of β-hydroxyphenethylamine (1). $\tau_1$ = C(2)–C(3)–C(5)–C(6), $\tau_2$ = N(1)–C(2)–C(3)–C(5), and $\tau_3$ = H(7)–O(4)–C(3)–C(5)

**Table 1.** Proton affinities in kcal $mol^{-1}$ [a]

| | Basis set | | | |
|---|---|---|---|---|
| | STO-3G | 3-21G | 3-21G(*) | Exp.[b] |
| $NH_3$: | 259.4 | 227.0 | 227.0 | 205.0 |
| $H_2O$: | 228.8 | 191.7 | 191.7 | 173.0 |
| $NH_2SO_2Me$ (at O): | 293.0 | 217.3 | 204.7 | |
| $NH_2SO_2Me$ (at N): | 249.6 | 197.7 | 193.6 | |

[a] All molecules are in structures fully optimized with the indicated basis set. [b] M. M. Szczesniak and S. Scheiner, *J. Chem. Phys.*, 1982, **77**, 4586; S. Scheiner, M. M. Szczesniak, and L. D. Bigham, *Int. J. Quantum Chem.*, 1983, **23**, 739.

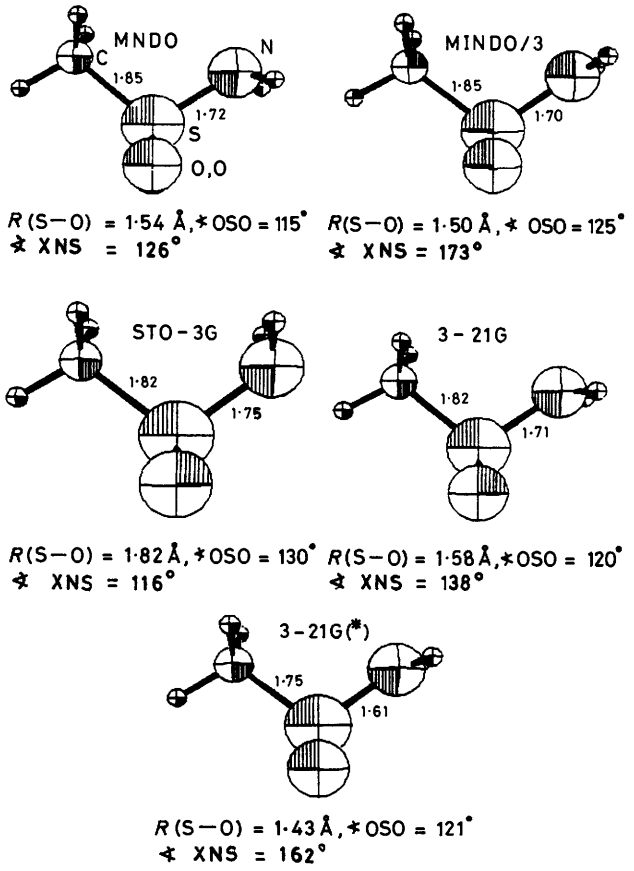



**Figure 2.** Optimized structures of methanesulphonamide. X is a point along the bisector of the angle HNH

**Table 2.** Interaction energy (in kcal mol$^{-1}$) with $OH^-$

| Structure | Method of calculation | | |
|---|---|---|---|
| | STO-3G | 3-21G | 3-21G(*) |
| $NH_3$ | 69.9 | 37.2 | 37.2 |
| $H_2O$ | 72.8 | 54.8 | 54.8 |
| $NH_2SO_2Me$ | 130.1 | 106.4 | 97.6 |

bility can be explored by comparing the proton-donating ability of the isolated MS and $H_2O$ (as a model for OH) molecules.

Using $OH^-$ as a model for an electron-rich region in the receptor, we simulated the interaction of these groups as proton donors to $OH^-$. Table 2 shows the interaction energies of $NH_3$, $H_2O$, and MS with the $OH^-$ group. In each basis set we performed a full optimization of all the geometrical parameters. The interactions of $H_2O$ and $NH_3$ with $OH^-$ have been studied by others, *e.g.* ref. 15. In all three basis sets $H_2O$ is predicted to be a better proton donor (higher interaction energy) than $NH_3$. For example, with the 3-21G(*) basis set the interaction energy of $H_2O$ with $OH^-$ is 54.8 kcal mol$^{-1}$ as compared with 37.2 kcal mol$^{-1}$ for $NH_3$. From Table 2 we also see that the proton-donating ability of MS is significantly better than that of $H_2O$, *i.e.* in the 3-21G(*) basis set the interaction energy of $OH^-$ with MS is 97.6 kcal mol$^{-1}$ as compared with 54.8 kcal mol$^{-1}$ for $H_2O$. In fact, using $OH^-$ as a model for the proton acceptor results in a complete transfer of the proton from MS to the $OH^-$ (to form $H_2O$) in the optimization. This suggests that in compounds such as the β-methylsulphonylaminophenethylamines, the inability of the MS group to act as a proton donor is not supported as a possible explanation for the reduction in activity as compared with the β-hydroxy compounds. In such situations other explanations could be considered. For example, consistent with the better proton-donating ability of MS compared with $H_2O$ predicted here, for the β-methylsulphonylamino compounds, the MS proton could be implicated in forming a strong intramolecular hydrogen bond with the side-chain amine. This could eliminate some other necessary interaction required for receptor binding. Alternatively, the MS may be ionized prior to the drug/receptor interaction and for that reason it will not always be a suitable replacement for an OH group, *e.g.* a proton donor. Other effects such as steric or conformational (see below) should also be considered. In drug/receptor interactions, the ability of MS to replace OH when present on a phenyl ring[1-3] contradicts some of these arguments. However, it is possible that the relative proton-donating abilities of the OH and MS groups are differentially affected when placed on a phenyl ring *vs.* an alkyl region.

*Influence of MS as a Substituent.*—The MS group is also expected to have a direct influence on the conformational properties of the parent compound which could, in turn, alter the mode of interaction with a receptor. Full *ab initio* optimizations of such compounds, using extensive [*e.g.*, 3-21G(*) or larger] basis sets are usually prohibitively large in their need for computational resources. For that reason we investigated the reliability of two semiempirical quantum chemical schemes, MNDO and MINDO/3. Using β-hydroxyphenethylamine and β-methylsulphonylaminophenethylamine again as sample compounds, we studied portions of these molecules which are (i) sufficiently large to represent regions for which an accurate description is necessary for reliability of a computational scheme while (ii) sufficiently small to allow *ab initio* calculations in sufficiently extensive basis sets to be used for calibration purposes.

(a) 2-*Hydroxyethylamine*. An important aspect in a proper description of the compounds discussed above is the ability accurately to describe any possible intramolecular hydrogen bond such as one between the side-chain OH and the terminal amine in β-hydroxyphenethylamine. Here we have taken 2-hydroxyethylamine as a model for this portion of the β-hydroxyphenethylamine.

**Table 3.** Energy differences[a] (in kcal mol$^{-1}$) between the *gauche* and *trans* forms of 2-hydroxyethylamine

| Method of calculation | Method of structure optimization | | | |
|---|---|---|---|---|
| | MNDO | MINDO/3 | STO-3G | 3-21G |
| MNDO | 1.17 | | | |
| MINDO/3 | | 3.42 | | |
| STO-3G | 0.88 | −3.07 | 2.37 | |
| 3-21G | 1.31 | −4.68 | 4.75 | 4.03 |

[a] Values are the energy of the *trans* form minus the energy of the *gauche* form.

The difference between the MNDO and MINDO/3 results in the *gauche* and *trans* forms of 2-hydroxyethylamine can be seen in Table 3 where we compare the relative energies of the *gauche* and *trans* forms of 2-hydroxyethylamine. From the diagonal entries we see that each method predicts the *gauche* form to be more stable when using its own structure. The relative stability of the *gauche* form is 1.2, 3.4, 2.4, and 4.0 kcal mol$^{-1}$ in the MNDO, MINDO/3, STO-3G, and 3-21G calculations, respectively. If we use the 3-21G energies as our standard (last row in Table 3) we see that the *gauche* form is more stable by 4.0 kcal mol$^{-1}$ when using its own (3-21G) structures and by 4.8 and 1.3 kcal mol$^{-1}$ when using the STO-3G and MNDO structures. However, when the MINDO/3 structures are used in the 3-21G calculations, the *gauche* form is less stable by 4.7 kcal mol$^{-1}$. This qualitative difference in the relative energy of the *gauche vs. trans* form is repeated when the MINDO/3 structures are used in the STO-3G calculations. The source of the discrepancy in the MINDO/3 results is evident from an examination of the structures of the *gauche* and *trans* forms obtained with each of the methods (Figure 3). All of these methods give qualitatively similar results for the structures of the *trans* form. Both of the *ab initio* methods predict a hydrogen bond between the hydroxy proton and the amine. The 3-21G results suggest a greater tendency (shorter length) for this hydrogen bond (2.17 Å). The MNDO structure of the *gauche* form has the hydroxy proton rotated slightly away from the amine to give an H ··· N length of 2.81 Å, but still close enough to allow for some stabilization due to hydrogen bonding in the STO-3G or 3-21G calculations. However, the MINDO/3 structure of the *gauche* form has the hydroxy proton rotated completely away from the amine. This prevents stabilization due to hydrogen bonding when the MINDO/3 structure of the *gauche* form is used in an STO-3G or 3-21G calculation and thereby causes a concomitant reversal of the relevative energies of the *gauche* and *trans* forms. These types of problems with the MNDO and MINDO/3 methods are inspiring the development of new semiempirical schemes.[16] The results for 2-hydroxyethylamine indicate that its MNDO structures are more reliable than its MINDO/3 structures. This is in contrast to our results for MS (above).

(b) 2-*Methylsulphonylaminoethylamine*. We show in Table 4 the results of calculations for 2-methylsulphonylaminoethylamine (2-MSEA) as a model compound. Analysis of the reliability of the different methods used here would be expected to reflect the findings summarized above.

The energy differences for the *trans* and *gauche* conformers of MS is within *ca.* 0.5 kcal mol$^{-1}$ of the 2-hydroxyethylamine values in the MNDO, STO-3G, and 3-21G calculations.

The MINDO/3 results for MS are different from those for 2-hydroxyethylamine because the dramatic absence of the intramolecular hydrogen bond in the MINDO/3 optimization of the *gauche* form of 2-hydroxyethylamine does not occur with 2-MSEA (see Figure 4).

Thus, the distance from the proton on the sulphonamide nitrogen to the side-chain amine is predicted to be 2.81 Å by the MINDO/3 optimization. This value is 2.66, 2.31, 2.18, and 2.21 Å for the MNDO, STO-3G, 3-21G, and 3-21G(*) optimizations, respectively. The 3-21G(*) value for the difference between the *gauche* and *trans* conformers is similar to the 3-21G value (3.38 *vs.* 3.70 kcal mol$^{-1}$, respectively).

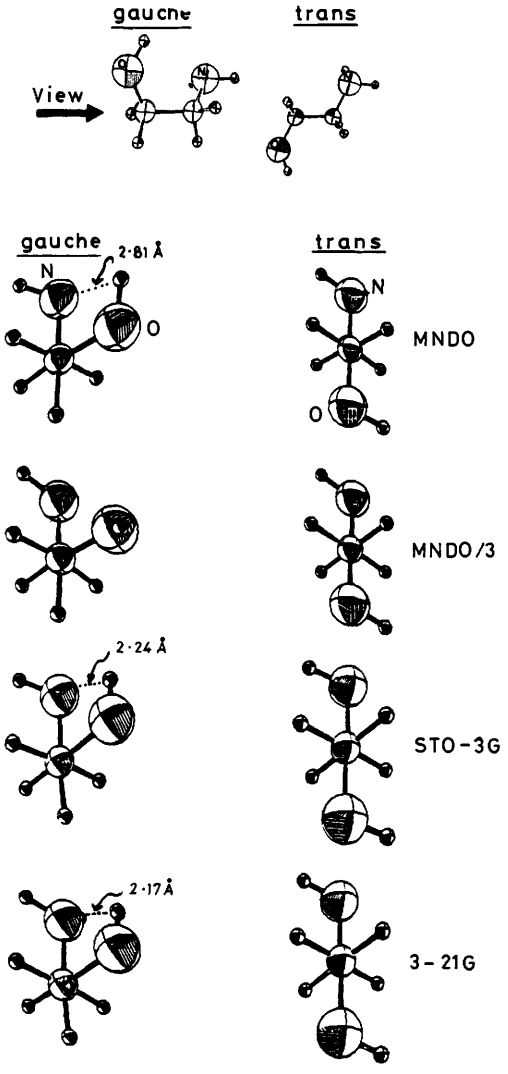



**Figure 3.** Optimized structures of 2-hydroxyethylamine

(c) *β-Hydroxyphenethylamine and β-methylsulphonylaminophenethylamine.* In light of the comparisons of the fragments given above, it is interesting to compare the results of MNDO and MINDO/3 calculations for β-hydroxyphenethylamine and β-methylsulphonylaminophenethylamine. Calibrations with *ab initio* calculations using extended basis sets were not possible for these large systems because of limitations of resources. Nevertheless, some interesting observations can be made. Table 5 highlights the structures of these two compounds with the MNDO and MINDO/3 calculations,[4] and Table 6 gives the relative energies of STO-3G calculations with the MNDO and MINDO/3 structures.

From Table 6 we see that the STO-3G calculations indicate that the MNDO structure of β-hydroxyphenethylamine is more reliable. The energy difference of the STO-3G//MNDO *vs.* the STO-3G//MINDO/3 calculations, 14 kcal mol$^{-1}$, is comparable to the 11 kcal mol$^{-1}$ value obtained in the similar comparison of the *gauche* conformer of 2-hydroxyethylamine using the *gauche* form of the side-chain. If we add to this 11 kcal mol$^{-1}$ the 22 kcal mol$^{-1}$ difference in energy of the STO-3G//MNDO *vs.* STO-3G//MINDO/3 results for MS we obtain a value close to the 30 kcal mol$^{-1}$ difference in energy for the similar comparison of β-methylsulphonylaminophenethylamine in Table 6. Thus the preference of the STO-3G calculations for MNDO over MINDO/3 structures found in the fragments seems to be reflected in these larger compounds. It should be recalled, however, that the STO-3G results themselves, as shown above, are questionable when second-row atoms are involved.

In spite of the differences between the MNDO and MINDO/3 results for the fragments described earlier and for these compounds as described in the previous paragraph, the overall conformations obtained with these two methods are very similar (Table 5). The largest difference between the MNDO and MINDO/3 structures is in the angle $\tau_3$ for β-methylsulphonylaminophenethylamine with values of 156.8°

**Table 4.** Energy difference[a] (in kcal mol$^{-1}$) between the *gauche* and *trans* forms of 2-methylsulphonylaminoethylamine

| Method of calculation | Method of structure optimization | | | | |
|---|---|---|---|---|---|
| | MNDO | MINDO/3 | STO-3G | 3-21G | 3-21G(*) |
| MNDO | 1.67 | | | | |
| MINDO/3 | | 1.23 | | | |
| STO-3G | 1.91 | −0.22 | 1.89 | | |
| 3-21G | 3.25 | 1.54 | 5.12 | 3.70 | |
| 3-21G(*) | 2.82 | 1.42 | 5.75 | 3.67 | 3.38 |

[a] Values are the energy of the *trans* form minus the energy of the *gauche* form.

**Table 5.** Optimized structures of β-hydroxyphenethylamine and β-methylsulphonylaminophenethylamine[a]

| Dihedral angle (°) | β-Hydroxyphenethylamine | | β-Methylsulphonylaminophenethylamine | |
|---|---|---|---|---|
| | MNDO | MINDO/3 | MNDO | MINDO/3 |
| $\tau_1$ | −107.1 | −109.0 | −104.2 | −113.5 |
| $\tau_2$ | 175.5 | 173.8 | 175.1 | 175.6 |
| $\tau_3$ | 158.2 | 158.0 | 156.8 | 96.1 |
| Distance (Å) | | | | |
| H(7)–N(1) | 2.63 | 2.76 | 2.55 | 2.94 |

[a] See Figure 1 for definition of parameters for β-hydroxyphenethylamine. For β-methylsulphonylaminophenethylamine, O(4) is replaced by N(4) in the definition of $\tau_3$; $\tau_1$ and $\tau_2$ are unchanged.

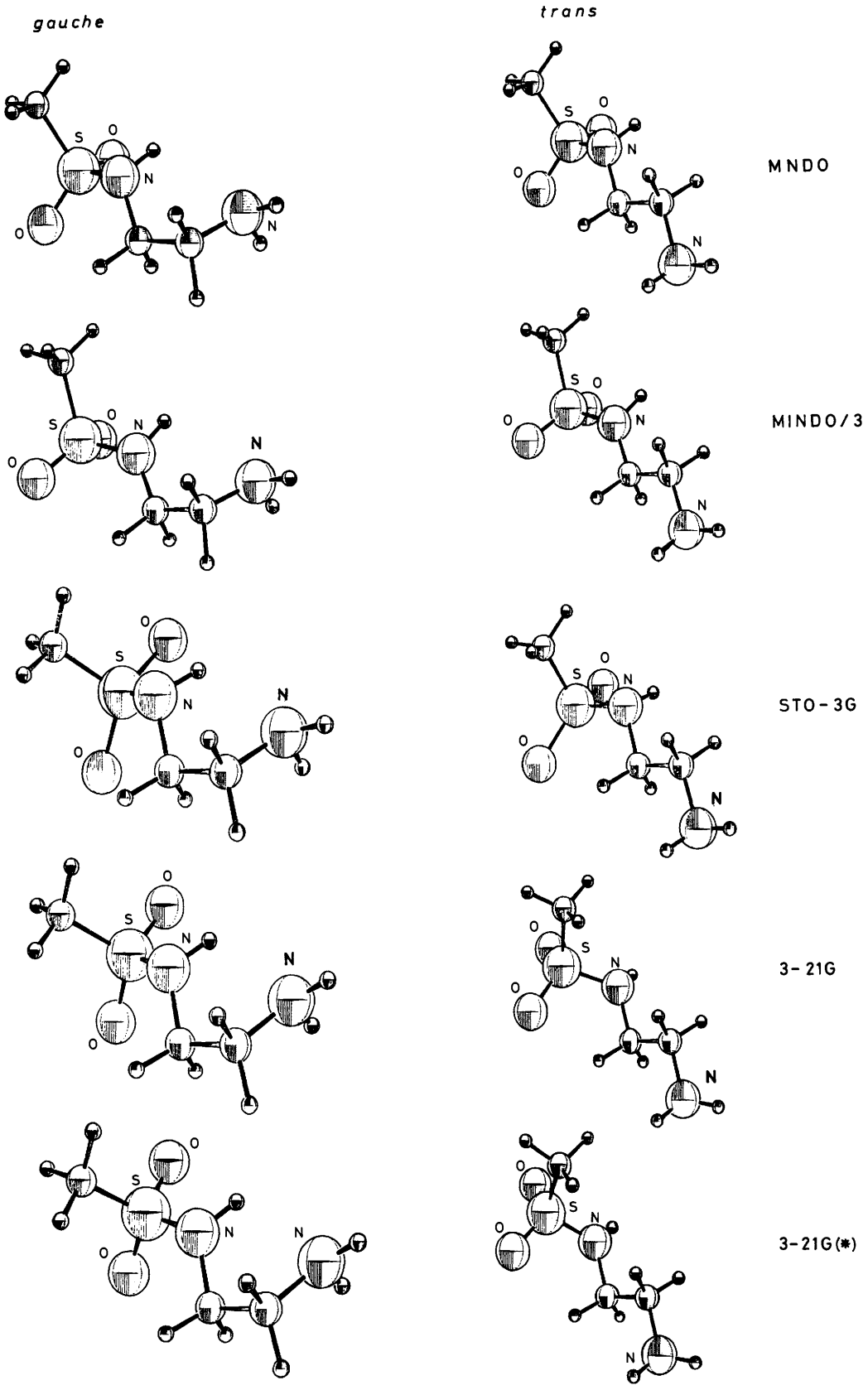



**Figure 4.** Optimized structures of 2-methylsulphonylaminoethylamine (2)

**Table 6.** Total energies calculated with the STO-3G basis set

| Geometry | | |
|---|---|---|
| MNDO | −433.179 739 a.u. | −992.775 475 a.u. |
| MINDO/3 | −433.156 771 a.u. | −992.727 315 a.u. |
| Difference | 14 kcal mol$^{-1}$ | 30 kcal mol$^{-1}$ |

and 96.1° for the MNDO and MINDO/3 results, respectively. This results in a slightly longer H(7) to N(1) distance for the MINDO/3 calculations, which is consistent with the poorer description of hydrogen bonding by MINDO/3 observed above in 2-hydroxyethylamine and again parallels the results for 2-MSEA. The MINDO/3 value of $\tau_3$ also results in a greater overlap between the two oxygen atoms and the π-orbitals of the phenyl ring which may actually be the major source of the difference. An analysis of this interaction using extended *ab initio* methods is planned as a separate work.

There is also very little difference between the hydroxy and MS compounds. As indicated previously,[4] this may not be sufficient to rule out conformational arguments for the inactivity of these MS compounds on β-adrenergic receptors. These lowest-energy (based on MNDO and MINDO/3) conformers may not correspond to some requisite conformer for activity which may be inaccessible, *e.g.* because of strong intramolecular hydrogen bonds or alternatively MS group to phenyl group stabilizations. Even the lowest-energy conformations may be different when extensive *ab initio* methods are used. In addition, purely bulk steric explanations are possible in that system.

## Conclusions

The conclusions from calculations and insights into drug action are very sensitive to the methods used. Direct calculations of proton affinities or proton-donating abilities show that they are dependent on the basis set used and can change the rank order of these properties in a series of compounds. This dependence on the basis set is true of the structures as well. The variation in the results is particularly evident when second-row compounds are studied *ab initio*. These differences in the reliability of *ab initio* results imply that an inappropriate choice of an *ab initio* method as a standard can result in misleading evaluations of semiempirical methods, and suggest further calibrations with more extensive basis sets.[14] For the examples given here, MINDO/3 is less reliable for treating the conformation of 2-hydroxyethylamine but gives a more reliable representation of the structure of the MS group.

Three possible explanations for the inactivity of 2-methylsulphonylaminophenethylamine relative to 2-hydroxyphenethylamine have been examined here: (i) the MS group may compete with the amine as the cationic site of the ligand; (ii) the MS group may not be as effective a proton donor as the OH group; and (iii) the MS group alters the ethylamine side-chain conformation. The 3-21G(*) calculations predict that $NH_3$ has a higher proton affinity than MS, which suggests that the side-chain amine would be preferentially protonated in β-methylsulphonylaminophenethylamine. The 3-21G(*) calculations also predict that the MS group is an even better proton donor when $OH^-$ is used as a model electron-rich site. Finally, the MNDO and MINDO/3 calculations give similar structures for β-hydroxyphenethylamine and β-methylsulphonylaminophenethylamine. Thus, three hypothesis examined here are not supported by the calculations. An explanation of the inactivity of the MS compounds would therefore require further study.

Because the MS group is often used as a substituent to replace OH on a conjugated ring system, it would be interesting to perform analogous computational studies of the MS group (and the OH group) on a phenyl ring.

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