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# Angular Dependence of the Interaction Energy Between the N Lone Pair of Amines and a Proton: Relevance to Drug–Receptor Systems

**VERA M. KOLB ˣ and STEVE SCHEINER**

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**Abstract** □ *Ab initio* molecular orbital calculations with a 4-31G basis set have been performed to study the angular dependence of the interaction energy between a lone electron pair of nitrogen and a proton. In this study ammonia and trimethylamine were used as models of biologically active amines. A proton was used as a model of an electrophilic site at the receptor. Results obtained confirm previous indications that the energy required to bend the proton from the lone pair direction decreases markedly as the two species are further separated from one another. Implications regarding the interactions of drugs and hormones at specific receptors are discussed.

**Keyphrases** □ Interaction energy—nitrogen lone electron pair of amines and a proton, angular dependency, drug–receptor systems □ Drug–receptor systems—interaction energy of the nitrogen lone electron pair of amines and a proton, angular dependency □ Amines—biologically active, interaction energy of the lone electron pair and a proton, angular dependency

Many hormones and drugs elicit their biological response through interactions with specific receptors (1–10). These interactions are typically weak, reversible, and specific (11) and, in addition, do not involve covalent bonding (1, 2, 8, 9). Many such interactions are of the electrophile–nucleophile type between sterically fixed groups. Because the nucleophilic pharmacophore frequently contains nitrogen at a critical position, we focus here specifically on the nature of the interaction of nitrogen with an electrophile.

One way nitrogen could interact with the specific electrophilic center at the receptor is *via* its lone electron pair. Such a mechanism has been suggested for opiate–receptor interactions (12–15). The influence of the directionality of the lone pair of biologically active amines on their activity has been demonstrated experimentally in some cases (12). One may envisage the most productive interaction as that in which the N lone pair is aligned exactly in the direction of the electrophilic site. This concept of amine–receptor interaction is illustrated in Fig. 1, which schematically depicts the binding of a (tertiary) amine to its receptor. Both the amine molecule and the electrophilic site are visualized as being sterically fixed at the receptor. We consider the distance between the N lone pair and the electrophilic site as longer than the normal bonding distance, since covalent bonding of nitrogen to the receptor does not occur (1). Figure 1A shows a perfect fit between the N lone pair and the electrophilic site. Figure 1B depicts a case of a substituted amine whose substituent (shown as a "bump" at the left-hand side of the molecule) interferes with the proper fit with the receptor cavity. There may of course be other factors leading to poor fit, and the effect shown in Fig. 1B is used only as an example. The repulsion between the substituent and the receptor cavity causes a small tilting of the molecule, which changes the position of the nitrogen atom and, therefore, its lone electron pair, relative to the electrophilic site. The N lone pair forms a "bent" complex with the electrophilic site.

Since the activity of the amine depends on the nucleophile–electrophile complexation, it is very important to learn about the energetics of the "bent" complexation of

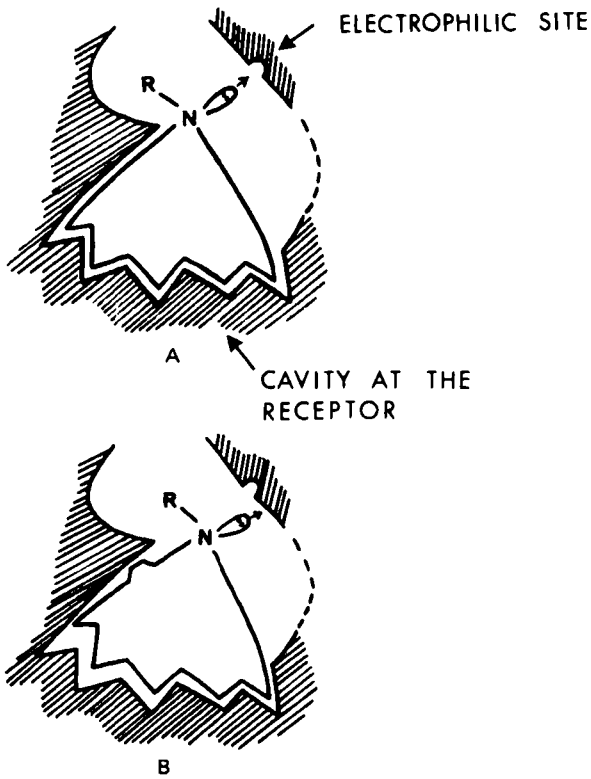


**Figure 1**—*Schematic representation of the binding of a biologically active (tertiary) amine to its receptor. Key: (A) perfect fit between the amine and its receptor; (B) less than perfect fit due to presence of a substituent (shown as bump on left of molecule).*

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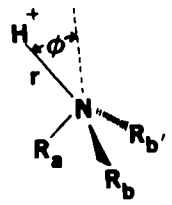


R = H , $CH_3$

*Scheme I*

the N lone pair (Fig. 1B) as compared with the "straight" complexation (Fig. 1A). The knowledge acquired about this problem may help to predict the activity of the derivatives of active amines and to understand better the mechanism of action of biologically active amines in situations where they are sterically restricted at the receptors.

Specifically, we wanted to determine the effects of the relative steric disposition of the nitrogen lone electron pair and an electrophilic site on the energetics of the interaction at distances longer than the normal bonding distance. Quantum chemical methods are particularly well suited for this purpose, since the relative orientations of molecules may be precisely specified. In addition, the wave functions may be analyzed to determine electron densities at various regions in the space between the two molecules to provide insights concerning the interaction. To perform *ab initio* calculations it was necessary to model the usually large biomolecules by smaller representative systems. Ammonia and trimethylamine were chosen as models of the nitrogen-containing portion of a biologically active amine. The proton, a spherically symmetrical species with no intrinsic steric requirements, was chosen as the simplest model for an electrophilic site at the receptor (the nature of such sites is generally poorly understood).

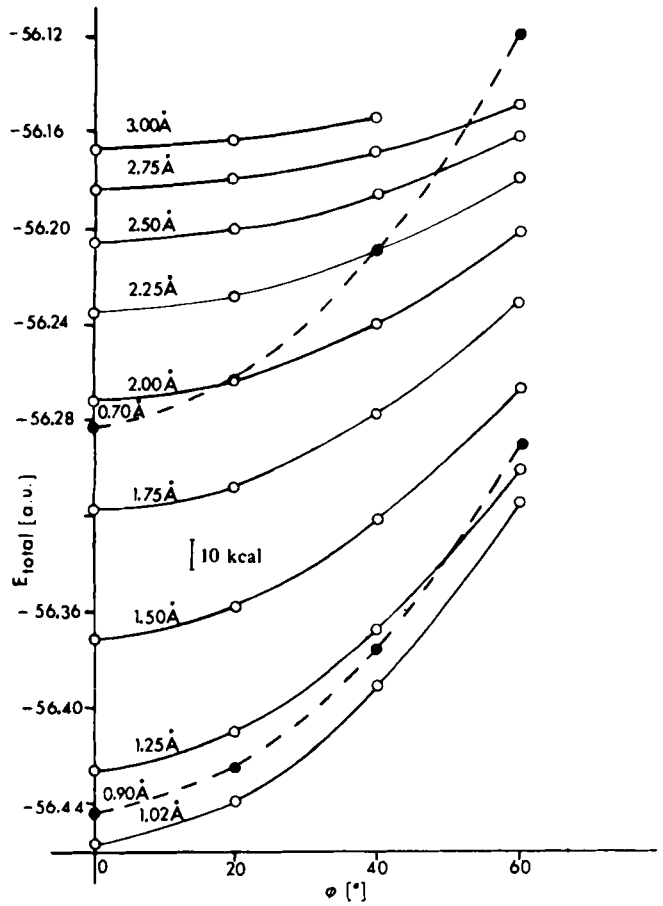


**Figure 2**—*Dependence of total energy* E *of the* $(H_3N\cdots H)^+$ *system on angle* $\phi$ *for various distances* r. *Filled circles and dashed lines indicate that* r *is shorter than the equilibrium distance* r = 1.02 Å. E(r = ∞) = −56.10249 a.u.

**Table I—Angular Dependence of the Total Energy of the $(H_3N\cdots H)^+$ and $((CH_3)_3N\cdots H)^+$ Systems**

| r, Å | φ, ° | ΔE, kcal/mol[a] $(H_3N\cdots H)^+$ | ΔE, kcal/mol[a] $((CH_3)_3N\cdots H)^+$ |
|---|---|---|---|
| 1.02 | 20.0 | 11.6 | |
| | 40.0 | 42.2 | |
| | 60.0 | 90.8 | |
| 1.20 | 20.0 | 10.4 | 11.5 |
| | 40.0 | 38.4 | 46.3 |
| | 60.0 | 81.1 | |
| | −20.0 | 6.5 | 11.0 |
| 1.50 | 20.0 | 8.4 | |
| | 40.0 | 31.4 | |
| | 60.0 | 66.0 | |
| 1.75 | 20.0 | 6.9 | 8.8 |
| | 40.0 | 25.8 | 35.3 |
| | 60.0 | 54.7 | |
| | −20.0 | 4.3 | 8.3 |
| 2.00 | 20.0 | 5.6 | |
| | 40.0 | 20.8 | |
| | 60.0 | 44.5 | |
| 2.25 | 20.0 | 4.5 | 6.1 |
| | 40.0 | 16.6 | |
| | 60.0 | 35.7 | |
| | −20.0 | 2.9 | 5.7 |
| 2.50 | 20.0 | 3.6 | |
| | 40.0 | 13.3 | |
| | 60.0 | 28.5 | |
| 2.75 | 20.0 | 2.9 | |
| | 40.0 | 10.6 | |
| | 60.0 | 22.8 | |
| | −20.0 | 1.9 | |
| 3.00 | 20.0 | 2.4 | |
| | 40.0 | 8.5 | |

[a] $\Delta E = E(\phi) - E(0)$.

## EXPERIMENTAL

Molecular orbital calculations were carried out within the *ab initio* restricted Hartree–Fock formalism. The GAUSSIAN-70 package of computer codes (16) was used to construct molecular orbitals as linear combination of atomic orbitals. The split valence–shell 4-31G basis set (17) was used rather than a minimal basis set, since the former provides greater flexibility to the valence orbitals and is expected to furnish a more realistic picture of long-range interactions between the amine and the proton than would the latter.

The experimentally determined geometries of ammonia (18) and trimethylamine (19) were used in our calculations. Ammonia belongs to the $C_{3v}$ point group and has $r$(N—H) = 1.01 Å and $\theta$(HNH) = 106.7°. The N—C bond distances in trimethylamine are 1.45 Å and the $\theta$(CNC) is 110.9°. Each methyl group is staggered with respect to the other two C—N bonds.

A proton was placed at various positions relative to the amines. As shown in Scheme I, these positions are characterized by the N—$H^+$ distance $r$ and $\phi$, the angle between the N—$H^+$ axis and the $C_{3v}$ symmetry axis of the $R_3N$ molecule. (The latter axis coincides with the expected direction of the N lone pair.) A positive value of $\phi$, shown in Scheme I, indicates a bend of $H^+$ toward $R_a$, while a negative value corresponds to a bend in the opposite direction.

The variation of the total energy of the $(H_3N\cdots H)^+$ system with changing $\phi$ is illustrated in Fig. 2 for values of $r$ between 0.70 and 3.0 Å. Dashed lines represent curves for $r < 1.02$ Å, the equilibrium N—H bond length. For each value of $r$, the lowest energy structure is that with $\phi$ = 0°, in which the proton lies directly along the $C_3$ symmetry axis of $NH_3$. Increasing $\phi$ results in a monotonic increase in the energy corresponding to a less stable complex. The sensitivity of the energy to $\phi$ decreases as $r$ is increased. For example, for $r$ = 1.02 Å the $(H_3N\cdots H)^+$ complex with

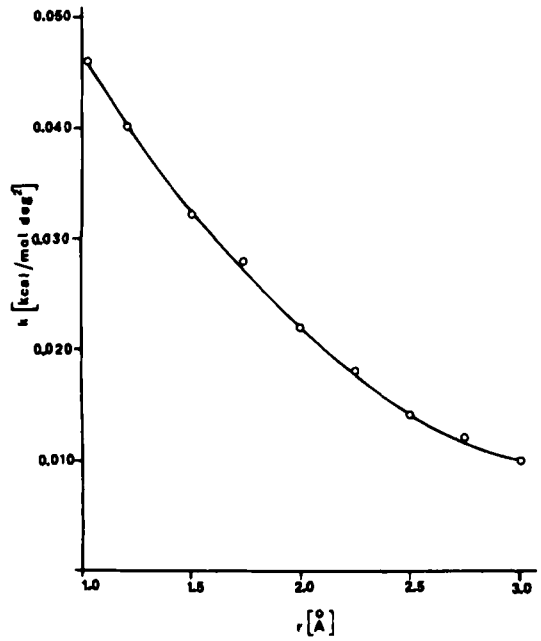


**Figure 3**—*Dependence of the bending force constant* k *on distance* r *for the* $(H_3N\cdots H)^+$ *system.*

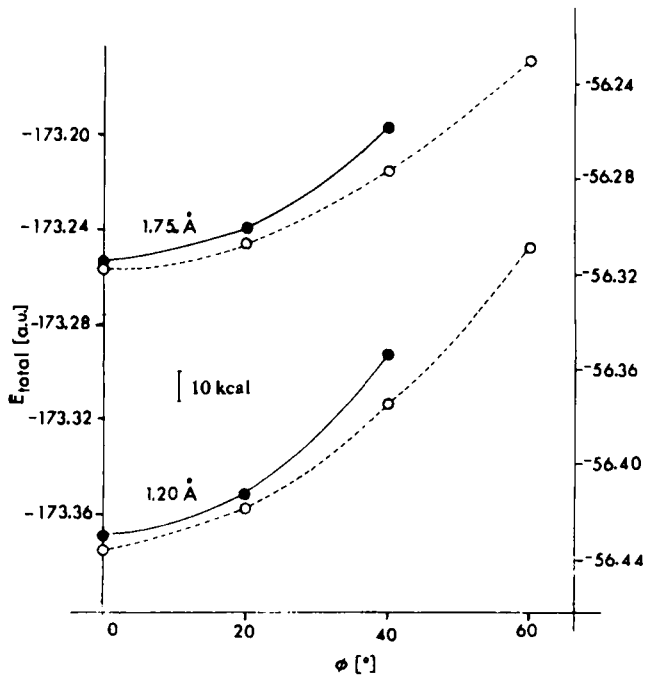


**Figure 4**—*Dependence of total energy* E *of the* $((CH_3)_3N\cdots H)^+$ *system on angle* $\phi$ *for two distances* r (● *and* —, *left ordinate). Also shown are the corresponding values for* $(H_3N\cdots H)^+$ *for the same distances* r (○ *and* - - -, *right ordinate). For the* $((CH_3)_3N\cdots H)^+$ *system* E (r = ∞) = −173.00797 *a.u.*

the proton bent 20° off the $C_3$ axis is 11.6 kcal/mol less stable than that for $\phi = 0°$, whereas the analogous quantity is only 2.4 kcal/mol for $r$ = 3.0 Å. Additional data concerning the energetics of deformation for angles $\phi = 20°$, 40°, and 60° are presented in Table I. Each value of $\Delta E$ is defined as the difference in energy between the indicated value of $\phi$ and that for $\phi = 0°$. Fitting these data to a parabola for each value of $r$ *via* least-squares analysis yields the bending force constants, $k$ ($\Delta E = 0.5k\phi^2$). Figure 3 shows how these bending force constants decrease with increasing $r$.

Deformation energies for selected conformations of $((CH_3)_3N\cdots H)^+$ are listed in the final column of Table I. Figure 4 shows a comparison of the results for the latter system (solid line) with those for the $(H_3N\cdots H)^+$ system (dashed line) at $r$ = 1.20 and 1.75 Å. A strong similarity is clearly evident for the energetics of bending in the two amine systems. For values of $\phi > 20°$, we note that the energy for $((CH_3)_3N\cdots H)^+$ rises somewhat faster with increasing $\phi$ than does $(H_3N\cdots H)^+$. This difference is probably a result of steric repulsion between the incoming proton and the methyl hydrogen atoms of trimethylamine, which are not present in $NH_3$.

The deformation energy for trimethylamine is quite uniform in the + and − direction of $\phi$, as indicated by similar $\Delta E$ values for $\phi = 20°$ and $-20°$. This is contrary to the $(H_3N\cdots H)^+$ case, where the deformation energy for positive $\phi$ is noticeably greater than for negative angles. In the latter case the proton fits "in between" (in a staggered manner) two ammonia hydrogen atoms ($H_b$ and $H_{b'}$; see Scheme I) while for positive $\phi$, the proton is eclipsed with one hydrogen ($H_a$). Thus, the three $H^+$—H distances for $\phi = 20°$ and $r$ = 1.75 Å are 2.02, 2.44, and 2.44 Å, as compared with 2.52, 2.20, and 2.20 Å for $\phi = -20°$. For trimethylamine the hydrogen atoms are more uniformly distributed around the central nitrogen. The four shortest $H^+$—H distances in the $((CH_3)_3N\cdots H)^+$ system, again for $r$ = 1.75 Å, are 2.33, 2.33, 2.81, and 2.81 Å for $\phi = 20°$, which is very similar to the corresponding values of 2.37, 2.37, 2.73, and 2.73 Å for $\phi = -20°$.

## DISCUSSION

We have presented calculated results of the energetics of deformation of the amine–proton system. The preferred or lowest energy structure in each case is one in which the proton lies directly along the lone pair direction of the amine. (A similar conclusion was reached by Baird (20) for the interaction of $NH_3$ with both $NH_4^+$ and $NH_3$.) Calculated bending energies extended over a wide range of values, varying up to 90 kcal/mol for 60° bends at the equilibrium $r$(NH) distance of 1.02 Å for the $(H_3N\cdots H)^+$ system.

Our calculated results show a greatly diminished sensitivity of the amine–electrophile interaction energy to angular deformation as the distance between the two species is increased. Qualitatively similar conclusions may be reached by examination of the molecular electrostatic potentials in the vicinity of the amine group of morphines (21, 22). Although these potential maps include only nonperturbing effects of a unit charge and thereby neglect polarization, charge transfer, and exchange terms, the results indicate preferred binding of a positive charge along the lone pair direction of nitrogen. The maps (21, 22) further suggest that the decreasing sensitivity of the binding energy to angle at longer distances, found here for simple amines, is common to morphines as well. Thus, the formation of a bent complex may be only a little less favorable energetically than a "straight" complex at separations of perhaps 2.5 or 3.0 Å. For example, while a bend of 20° in the $(H_3N\cdots H)^+$ system leads to a deformation energy of 11.6 kcal/mol at 1.02 Å, the strain energy for a similar bend is only 2.4 kcal/mol at $r$ = 3.0 Å.

It is therefore important to consider what might be expected for the distance between the nucleophile and the electrophile at the receptor when the (noncovalent) interaction occurs. A distance of 2 Å was used in the "transition-state complex" between the propene nucleophile and a proton by Caramella *et al.* (23). Distances between nucleophiles and electrophiles of as long as 3 Å have been observed in crystal structure studies (24). Bürgi *et al.* interpreted these long distances as indicating nonbonded interactions of the donor–acceptor and dipole–dipole types (24). Therefore, distances between the amine nucleophile and electrophile of ≥2 Å at the receptor would not be an unreasonable estimate.

At interaction distances >2 Å, the lone pair and electrophile may be significantly misaligned without large deformation energies. For example, for the $(H_3N\cdots H)^+$ system, at $r$ = 2.0 Å, a bend of 15° from optimal orientation produces an energy increase of 3 kcal/mol, while the analogous bend yielding a similar increase at $r$ = 3.0 Å is 24°.

While it would be presumptuous to generalize our data on the $(H_3N\cdots H)^+$ and $((CH_3)_3N\cdots H)^+$ systems and claim that they are directly applicable to all nitrogen-containing drugs and hormones, we believe that our findings should be considered qualitatively when picturing the interaction of the N lone pair of biologically active amines with an electrophilic site at the receptor.

The fact that the difference in energy between a "bent" and "straight" complex may become very small for longer $r$ values does not support the orbital steering concept (25). The experimental (26) and theoretical (*e.g.*, 27) work of other investigators has already provided evidence which is not in agreement with the orbital steering concept.

Finally, we may note that our studies on angular dependence of the interaction between the N lone pair of amines with a proton complement

previous studies of the angular dependence of the interaction between nucleophiles and certain electrophiles which possess intrinsic steric requirements (27, 28), as well as electrophiles in general (20, 29–32).

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# NOTES

# Determination of the Average Molecular Weight of Nonionic Emulsifiers by Vapor-Phase Osmometry


**FRANCE GUAY and SUZANNE BISAILLON** ˣ



Received October 5, 1982, from the *Faculty of Pharmacy, University of Montreal, Montreal, Quebec, H3C 3J7, Canada.* Accepted for publication January 10, 1983.



**Abstract** □ Standard nonionic emulsifiers are heterogenous by nature. Their reported molecular weight is unreliable, especially when several lots of the product are used in a study. The number-average molecular weights of two nonionic emulsifiers, poloxamer 188 and polyoxyethylene(23) lauryl ether were determined by vapor-phase osmometry. This determination is essential when the concentration should be given in molarity rather than in weight per volume. A discrepancy was noted between the number-average molecular weights of two lots of poloxamer 188. That difference is taken into account prior to the establishment of any comparison of the behavior of the emulsifiers.



**Keyphrases** □ Poloxamer 188—number-average molecular weight, vapor-phase osmometry □ Polyoxyethylene(23) lauryl ether—number-average molecular weight, vapor-phase osmometry □ Vapor-phase osmometry—determination of number-average molecular weights, poloxamer 188, polyoxyethylene(23) lauryl ether


Standard nonionic emulsifiers are chemically impure, with a composite nature that confers specific properties which render them suitable for numerous applications such as emulsification, wetting, foaming, *etc.* Because of this particular feature, determination of the molecular weight of nonionic emulsifiers is complicated and the analytical




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