Isotope Effects on Gas Phase Reaction Processes.
# 2. Equilibrium Isotope Effects on the Proton Transfer Reactions of Methylbenzenes

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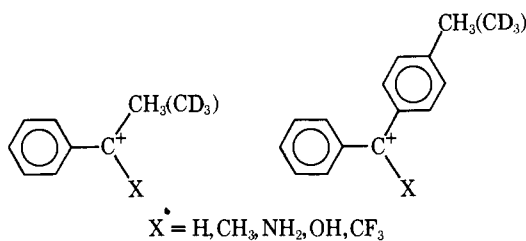
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Abstract: Gas phase pulsed ion cyclotron resonance spectroscopy has been employed to measure the energetic effects of CD_3 substitution on the proton transfer reactions of a number of simple methylbenzenes. Protonation of the light (CH_3 substituted) isotopic species of toluene is found to be significantly more favorable than the heavy variant, consistent with notions about the ability of a para methyl to hyperconjugate with the ring. Examination of the energies of the corresponding proton exchange reactions for *m*-xylene and mesitylene, relative to that for toluene, suggests the necessity for a different explanation for the isotope effect of an ortho methyl group. That is to say, rather than the expected enhancement in the preference for protonation of the light isotopic variant of these compounds, what is actually observed is a diminishment of that preference. The isotope effect on the proton transfer reaction of *o*-xylene is, within experimental error, identical to that for toluene, suggesting a negligible contribution to the total of a meta methyl substituent. The measured equilibrium isotope effect for the analogous reaction involving *p*-xylene is interpreted in terms of partial (or exclusive) protonation at the site of attachment of one of the methyl substituents.

The measured effects of remote deuterium substitution on the rates of solvolysis of systems such as α-phenylethyl and benzhydryl chlorides have been taken as strong evidence for the ability of CH linkages to stabilize the nascent center of positive charge.[2] Thus, *p*-methyl-α-phenylethyl chloride (I) solvolyzes 1.10 times as rapidly as the corresponding *p*-methyl-d_3 system;[2a] a somewhat smaller difference in rates ($k_H/k_{d_3} = 1.058$) has been noted for solvolysis for the para-substituted benzhydryl systems (II).[2b] Secondary deuterium
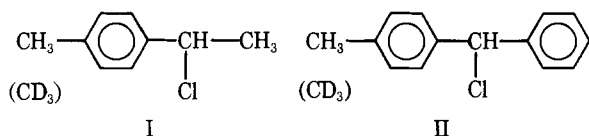
isotope effects on the ^{19}F NMR chemical shifts of ions have recently been reported.[3] Their magnitudes appear to correlate with the π donating ability of the substituent group $X(CF_3 > H > Me > OH > NH_2)$. The ability of an alkyl group to sta-


bilize a positively charged center has generally (and loosely) been termed hyperconjugation, and is usually rationalized in terms of the influence of quinoidal resonance structures of the form:
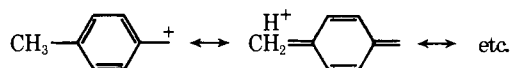

The detailed geometrical distorsions, which are implied in the writing of valence forms such as the above, are critical to an understanding of the measured deuterium isotope effects. They may be arrived at in an alternative (and more systematic) manner by use of simple perturbation molecular orbital theory.[4] Here we need to consider the consequences of interaction of the filled valence orbitals on a methyl group with the empty p-type function on a (partial) carbonium center. Two

symmetrical orientations of the methyl groups relative to a carbonium center are possible. In one, a single CH linkage remains in the "ring" plane; the other two bonds are symmetrically disposed above and below it. Here the CH_3 valence orbital of appropriate symmetry to interact with the vacant p function at C^+ is concentrated in a bonding manner along the two out-of-plane methyl CH linkages. The third, in-plane, CH bond is of incorrect symmetry, and makes no contribution to this particular valence orbital. The transfer of electron density (from methyl to the vacant p function) which results in the
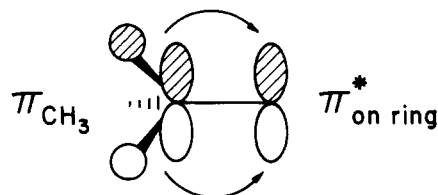

formation of a partial double bond between the alkyl substituent and the ring also leads to a decrease in the bonding character of the out-of-plane CH linkages and hence to their lengthening. The third, in-plane, CH remains unaffected. In addition, the antibonding character of the interaction between the out-of-plane CH's is lessened as a result of electron withdrawal. Hence one of the HCH bond angles (that between the two out-of-plane CH linkages) will decrease. The other possible conformation orients one of the CH linkages above and perpendicular to the surface of the ring and directs the other two
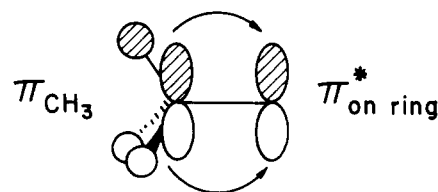
downward at 30° angles to the plane. Here electron withdrawal weakens (and hence lengthens) all three carbon–hydrogen bonds. Withdrawal of the methyl group's valence electrons also leads to two distinct angular distortions. For one, the angles that the two hydrogens below the plane make with the one above it should decrease in response to a lessening of the antibonding density between them. On the other hand, the angle connecting the equivalent pair of methyl hydrogens beneath

the plane would be expected to widen, indicative of a loss of bonding density.

Although the detailed geometries of such systems as protonated toluene or *p*-methylbenzyl cation are unknown at present (either from experiment or theory), quantitative ab initio molecular orbital calculations have been reported on the structures of a number of model compounds. Thus, STO-3G level calculations indicate that the geometries of the bisected and eclipsed ethyl cation[5] (model systems in which a methyl group is affixed to an unsubstituted carbonium center in each of the two symmetrical conformations discussed) are in complete accord with the predictions of the simple perturbation molecular orbital procedure. Theoretical carbon–carbon and methyl C–H bond lengths as well as one of the HCH bond angles for these systems are presented below. The calculated geometrical structure for ethane is also included for comparison. It should be realized that the difference in stabilities of these two limiting conformers of the ethyl cation should be very

<div align="center">

ethyl cation   ethane

eclipsed   bisected

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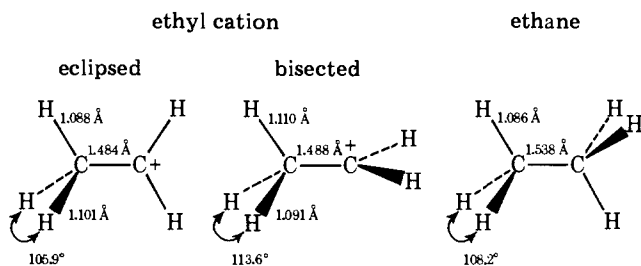
small, owing to the sixfold nature of the rotational potential. Thus, the real situation is best described not in terms of either of these possibilities but rather as a superposition of the two. The net result would then be a uniform lengthening of all three of the methyl's CH linkages, and a narrowing of the cone which encompasses them. Although the arguments based on resonance theory clearly suggest the former (bond lengthening), they provide no indication at all as to the accompanying angular distortions.

A related system on which detailed ab initio molecular orbital calculations have been performed is the *tert*-butyl cation.[4] Its structure, like that for the bisected ethyl cation, clearly shows the expected distortions: a shortening of the C–C linkages from normal single bond values (1.541 Å in propane at
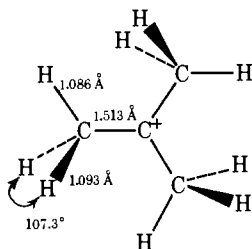

the same level of calculation;[5] 1.520 Å in propene), and a lengthening of the six out-of-plane C–H's (from 1.086 and 1.085 Å in propane and propene, respectively). The three in-plane carbon–hydrogen bonds remain largely unaffected. Finally the angular distortion predicted by the simple perturbation molecular orbital arguments is clearly in evidence. We suspect that the *tert*-butyl cation is a better model than ethyl for the size of the geometrical distortions to be anticipated in a system such as protonated toluene. This is simply because that here, as in protonated toluene, each methyl group "sees" only a third of the total positive charge.

As indicated earlier, the direction of the kinetic isotope effect in such processes as would be expected to result in the generation of considerable positive charge on a carbon center adjacent to a methyl probe is consistent with CH bond lengthening. That is to say, elongation of the methyl CH linkages, paralleled by a lessening of the associated force constants,
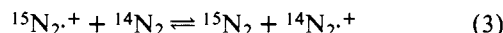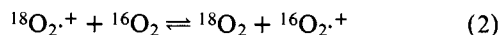
reduces the difference in the harmonic CH stretching frequencies between the heavy and light isotopic forms.

In the present paper we describe our attempts to evaluate the importance of CH hyperconjugation in the gas phase. In particular, we shall be interested in knowing if the energetic effects of methyl substituents on the proton affinity of benzene are explicable entirely in terms of stabilizing hyperconjugative interactions, or whether some alternative explanation as to their origin needs to be advanced. The key which we shall employ to decipher the mechanism by which methyl groups effect stabilization of positively charged centers will be the measurement of the energetics of proton transfer equilibria of the form,
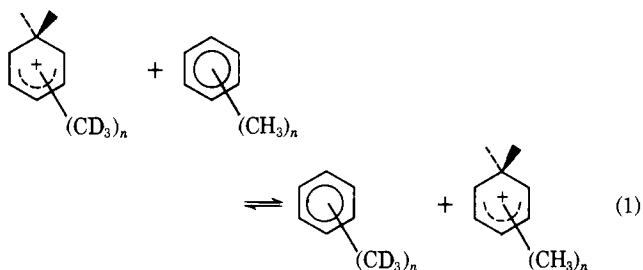
processes involving competition for protonation of an alkylated benzene and its fully (methyl) deuterated analogue.

We have already established[6] that the energetics of such equilibrium processes as (1) may be readily determined by gas phase ion cyclotron resonance (ICR) spectroscopy. In particular it was demonstrated that the equilibrium constants given by the ICR method for the charge transfer reactions

$$^{18}O_2 \cdot^+ + {}^{16}O_2 \rightleftharpoons {}^{18}O_2 + {}^{16}O_2 \cdot^+ \tag{2}$$

$$^{15}N_2 \cdot^+ + {}^{14}N_2 \rightleftharpoons {}^{15}N_2 + {}^{14}N_2 \cdot^+ \tag{3}$$

were, in the mean, very close to their statistical mechanical values. Furthermore, it was commented that the errors inherent to the method, two or three tens calorie/mole in ΔG°, are absolute, being caused primarily by uncertainties in the measurement of the partial pressures of the neutral molecules involved in the equilibria. Thus, although the precision of the measured gas phase equilibrium isotope effects is easily one and perhaps two orders of magnitude less than that attainable by solution phase techniques, it should be adequate for our purposes here.

Results and Discussion

Equilibrium constants for the proton transfer reactions 4–9 have been measured using pulsed ion cyclotron resonance techniques.[7] Since the alkyl benzenes protonate only very slowly, it was necessary to add to the system a fivefold excess of methyl mercaptan or arsine to function as a source of protons. Expressed in terms of free energies,

$$\Delta G^\circ = -RT \ln K$$

our data are presented in Table I.

ΔG° for reaction 4, that involving the proton transfer equilibrium between toluene and toluene-α-d_3, is determined as -328 ± 40 cal/mol. In agreement with the solution phase kinetic data on related systems such as I and II,[2a,b] and consistent with notions arising from the hyperconjugative model, ΔG° is negative for the reaction as written, indicating a preference for protonation of light isotopic species. As a check on the ICR method we have also measured ΔG° for reaction 5 in which toluene-α-d_1 and toluene-α-d_3 were equilibrated. As the three methyl group hydrogens in toluene are presumably equivalent on the time scale of the ICR experiment (100–1000 ms), we would anticipate that the free energy of reaction 5 should be two-thirds of that determined for reaction 4. Within

Table I. Isotope Effects on Gas Phase Proton Transfer Equilibria

Reaction	$\Delta G°$
(4)	-328 ± 40
(5)	-223 ± 28
(6)	-321 ± 34
(7)	-240 ± 9
(8a)	-185 ± 18
(8b)	
(9)	-175 ± 53

experimental error, the value obtained (-223 ± 28 cal/mol) satisfies this criterion.

$\Delta G°$ for the equilibrium proton transfer between mesitylene and mesitylene-α-d_9 (reaction 9) is -175 ± 53 cal/mol. Although the measured isotope effect is in the same direction as that for the analogous process 4 involving toluene, its magnitude is surprisingly small. This is unexpected because all evidence seems to indicate that the positive charge on a system such as protonated mesitylene is not localized on the para position alone. Rather, as is implied by valence structures of the form,
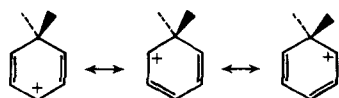

a portion of it resides on sites ortho to the position of protonation. Such a picture is also consistent with the π charge distributions found by a variety of molecular orbital calculations at the ab initio level. The notion that the ortho ring positions bear a significant part of the system's positive charge is also

supported by our recent investigations into the effects of methyl substituents on the proton affinity of benzene.[9] What was

found was that the stabilization imparted to protonated benzene by a single ortho methyl group (6.0 kcal/mol) was of almost equal magnitude to that resulting from a para CH_3 (7.2 kcal/mol). We are left then with a paradox. Whereas the same hyperconjugative arguments as applied to the case of toluene would lead to the conclusion that the additional methyl groups present in mesitylene would further the preference for protonation of the light isotopic species over the heavy, in fact what is actually observed is exactly the opposite.

In order to further our understanding of the origin of the isotope effect in mesitylene, or more precisely, the contribution of the two ortho methyl groups toward the total, we have examined the energy of the proton transfer reaction 7 involving the light and heavy isotopic variants of m-xylene. The value which results ($\Delta G° = -240 \pm 9$ cal/mol) is almost exactly half-way between those for the analogous proton transfer processes in mesitylene and toluene. The fact that the isotope effects caused by the first and second ortho methyl substituent are approximately the same might be taken as evidence for their electronic (as opposed to steric) origin. Therefore, if steric factors were a major consideration, we might expect that any increase in crowding in the vicinity of isotopic substitution as a result of protonation would lead to a shift in equilibrium toward the heavy ionic species.[10] This is opposite to the order which would be predicted on the basis of hyperconjugative arguments.
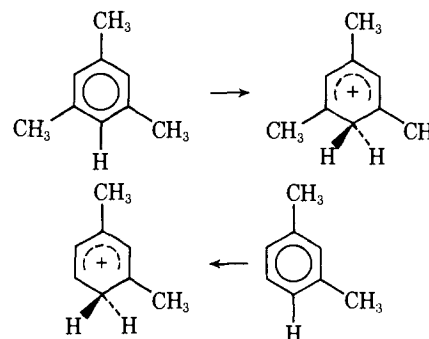

increase in crowding in mesitylene more extreme than that in m-xylene

In hope of uncovering the reason behind the difference in observed isotope effects, we have performed a series of quantitative molecular orbital calculations on ortho and para protonated toluene. The minimal basis ab initio STO-3G method has been employed, a full description of which has previously been given.[11,12] Of particular interest to us is the extent of geometrical distortion in the vicinity of the methyl group (that is to say, at the site of deuterium substitution) in these compounds. Thus, we have carried out optimization of a number of critical geometrical parameters, specifically the C_{methyl}–H and C_{methyl}–C_{ring} bond lengths.[13] Our results are given below. Although the distortions to the methyl CH linkages are small, being of the same order of magnitude as those already noted for the $tert$-butyl cation, they are in the direction required by
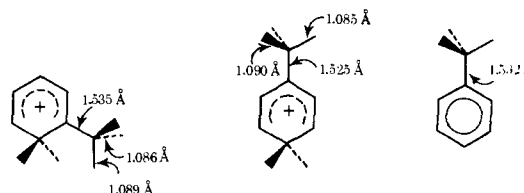
the simple perturbation molecular orbital arguments. More pertinent to the discussion at hand is the fact that the lengthenings noted for methyl groups ortho and para to the site of protonation are nearly the same. What the calculations suggest is that the only sizable difference between the two cases is in the length of the carbon–carbon bond connecting the methyl

substituent to the ring. In fact, whereas the CC linkage in para protonated toluene is predicted by the calculations to be slightly shorter than that in the hydrocarbon itself, an observation which is consistent with the notion of hyperconjugative interaction, that in the ortho protonated compound is actually longer. This latter distortion, opposite to that dictated on the basis of the simple hyperconjugative arguments, may be rationalized by realizing that the ortho ring position to which the methyl is attached undergoes significant rehydrization as a result of protonation. This is simply because incorporation of a nearly tetrahedral center into the six-membered ring of the protonated compound forces an opening of the neighboring CCC bond angles from 120° to approximately 126°. This results in a ring-substituent bond of enhanced p character (over sp^2 found in toluene) and hence of greater length. It is not
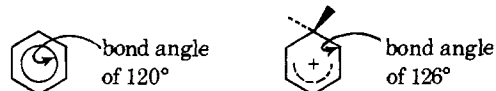
apparent to us at this time what effect such a bond lengthening will have on the isotope effect. We only wish to indicate that it appears to be the only significant point of difference in molecular geometry between systems in which a methyl group is substituted ortho and para to the protonation site.

Our assignment of the direction of the isotope effect in "ortho" protonated toluene, as that favoring formation of the heavy ion, is, of course, based on the notion of additivity. That is to say, it is arrived at by assuming that the isotope effect due to a methyl group para to the site of protonation in m-xylene or in mesitylene is the same as that for toluene. It is certainly possible that this basic assumption is in error, and, in fact, that the isotope effect shows extreme sensitivity to the detailed environment to which the methyl probe is attached.

The measured isotope effect on the protonation of o-xylene (-321 ± 34 cal/mol favoring formation of the light cation) is, within experimental error, identical with that for toluene itself. Assuming protonation at the 4 position,[9] this is entirely consistent with the organic chemist's notion that the distribution of positive charge in such systems is largely restricted to ortho and para sites, that is to say, that meta substituents do not play a major role in its dispersal.
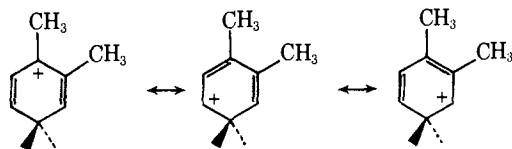

Table II summarizes our experimental estimates for secondary isotope effects incurred by replacement of a methyl group ortho, meta, or para to the site of protonation in toluene by a CD_3 moiety. Toluene protonates preferentially para to the methyl.[9] Thus, the isotope effects characteristic of the ortho and meta ring positions have been obtained by subtracting the magnitudes of the effects observed in m- and o-xylene, respectively, from that in toluene. Also tabulated are our previously reported energies of protonation of toluene (relative to benzene) ortho, meta, and para to the methyl. Only the
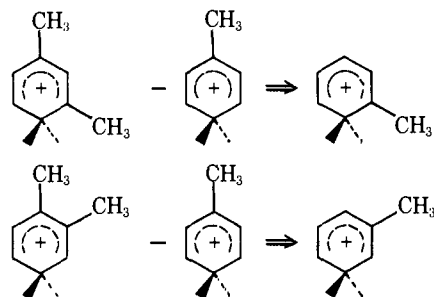

Table II. Secondary Isotope Effects and Relative Proton Affinities of Protonated Toluene

Position of protonation	Isotope effect,[a] cal/mol	Relative proton affinity,[b] kcal/mol
Ortho	88 ± 49	6.0 ± 0.2
Meta	7 ± 74	2.4 ± 0.2
Para	-328 ± 40	7.2 ± 0.2

[a] Value for para protonation is $\Delta G°$ for reaction 4; ortho and meta values obtained by subtracting this quantity from energies of reactions 7 and 6, respectively. See text for discussion. [b] $\Delta H°$ for reactions
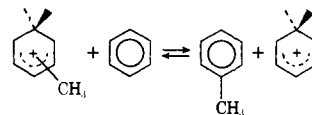
See ref 9 for a discussion.

lattermost has been obtained directly, the ortho and meta affinities being derived from proton transfer reactions involving m- and o-xylene, respectively. As has already been pointed out, the methyl group isotope effects do not parallel the associated proton affinities. Thus, whereas an ortho methyl group stabilizes protonated benzene to nearly the full extent of a para substituent, its isotope effect appears to be of far smaller magnitude and of opposite sign.

Finally, we have considered the magnitude of the secondary (CD_3) deuterium isotope effect on the proton transfer reaction 8 involving p-xylene. Recall that in an earlier publication[9] we indicated the apparent closeness in energy for protonation of p-xylene ortho to one CH_3 substituent and meta to the other (reaction 8a) or at the point of attachment to one of the methyl groups (reaction 8b). We concluded at that time by suggesting that measurement of the CD_3 isotope effect might prove of use in distinguishing between these two possibilities. Thus, assuming additivity of methyl group isotope effects, we would expect the energy of reaction 8a to be expressed in terms of the contributions of one ortho (88 ± 49 cal/mol) and one meta (7 ± 74 cal/mol) methyl group, that is to say, 95 ± 123 cal/mol in total. The isotope effect resulting from ipso protonation of p-xylene (reaction 8b) is somewhat more difficult to estimate. It would comprise of contributions from one methyl group para to the site of protonation, and another directly affixed to it. Although the former quantity may be assumed to be identical to that in toluene itself (-328 ± 40 cal/mol), we have at hand no data with which to precisely estimate the contribution to the total of the ipso methyl substituent. Perhaps the best we can do is to assume an isotope effect of the direction and order of magnitude as that found in the proton transfer reaction

$$\Delta G°(\text{per } CD_3) = 104 \pm 10 \text{ cal/mol}$$
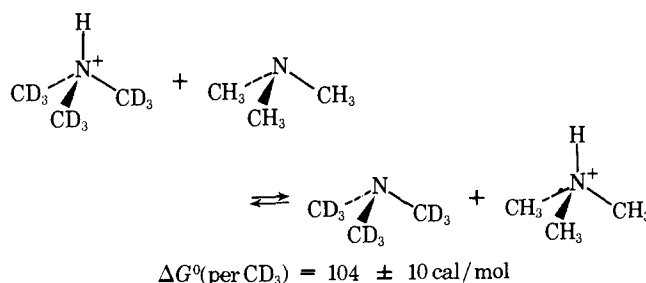
Thus, exclusive ipso protonation of p-xylene might (very roughly) be expected to lead to an isotope effect of $-328 \pm 40 + 104 \pm 10 = -224 \pm 50$ cal/mol. The value we actually observe, -185 ± 18 cal/mol, falls in between these two estimates. Although it is close enough to our rough estimate for the energy of reaction 8b to be explicable in terms of ipso protonation alone, it would appear that the measured value is evidence against reaction 8a being the exclusive reaction pathway. More

than likely the observed isotope effect arises from both reaction channels being operative, a notion which is consistent with the results of our previously reported quantitative molecular orbital calculations.[9]

Conclusions

The following conclusions may be drawn from the study reported in this paper:

1. The direction of the secondary deuterium isotope effects in proton transfer processes involving a variety of simple alkyl benzenes (e.g., toluene, the xylenes, and mesitylene) is consistent with the notion that a methyl group para to the site of reaction acts through hyperconjugation to stabilize the positive charge. The hyperconjugative arguments would lead to assignment of the same direction for the isotope effect of an ortho disposed methyl substituent. However, our measurements indicate for the ortho position the opposite, suggesting the dominance of other factors in determining the overall isotope effect.

2. Contributions to the total isotope effect caused by methyl groups meta to the protonation site appear to be very small. This is in line with the results of simple resonance theory, where in drawing the contribution valence structures
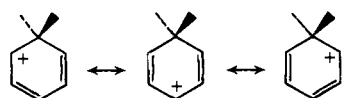
we imply that the molecule's positive charge resides largely on the ortho and para sites.

3. The measured isotope effect on the proton transfer reaction involving p-xylene seems to require ipso protonation of at least some (if not all) of the molecules.

Experimental Section

Toluene-α-d_1 was prepared by the method of Trevoy and Brown,[16] by reacting benzyl bromide (4 g) in THF (25 ml.) with LiAlD$_4$ (1 g) at room temperature. Toluene-α-d_3 and o- and m-xylene-α-d_6 were prepared by reacting benzene (10 ml) with AlCl$_3$ and CD$_3$I at 0 °C for 96 h.[17] Separation was effected by gas chromatography.[18] Mesitylene-α-d_9 was prepared as above except that the reaction mixture was heated to 100 °C for 3 h. The product was purified by gas chromatography. p-Xylene-α-d_6 was purchased from Aldrich.

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Determination of Precise and Reliable Gas Diffusion Coefficients by Gas Chromatography

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Abstract: A specially designed gas chromatograph has been tested for the measurement of the diffusion coefficient of methane in helium at 25 °C. Both the continuous elution and Knox's arrested elution techniques were used and the latter is considered the more reliable, yielding a value of 0.6735 averaged over seven arrested times with a standard deviation of 0.0008. The equation for the elution profile of an arrested elution peak is derived and experimental peaks fit this with a standard error near 7×10^{-4}. Uncertainty in the pressure measurement decreases the reliability of the result but a value of 0.674 ± 0.002 is confidently reported; this agrees well with other published data.

Gaseous binary molecular diffusion coefficients D_g are an important physical parameter in both basic and engineering research and in chromatographic theory. Various theoretical and experimental approaches are employed for their measurement and numerous reports have been published since the early years of this century. However, the results obtained from