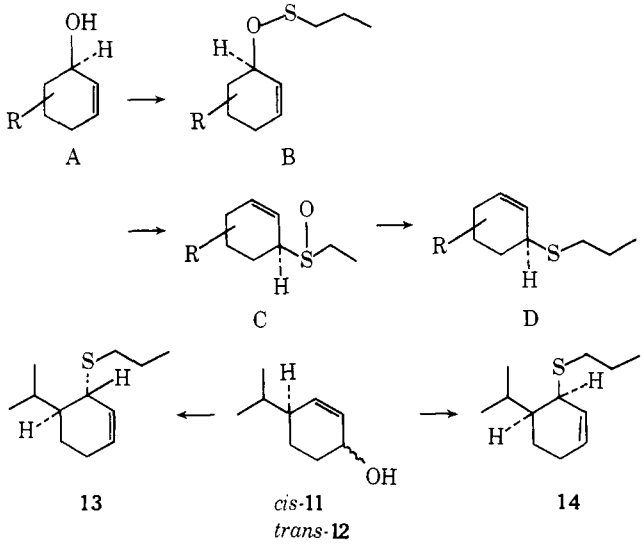


than these numbers imply because the starting dichlorobenzoate, in contrast to the earlier conclusion, was not entirely stable to the reaction conditions: the recovered ester fraction (~30%) was 20% rearranged.[14] This hypothesis was supported by carrying out the reaction for only 1 h: under these conditions of very low conversion (3.5% reaction). The two amines **2** and **4**, which made up 90% of the amine fraction, were formed in a 10:1 ratio in favor of **2**, the product of syn displacement. More definitive results were obtained by utilizing a more stable ester, **1**, R = 2,4,6-trimethylbenzoyl. Displacement with piperidine, *under conditions* (24 h, 130 °C; 25% completion) *which caused no rearrangement in the starting mesitoate or in the reaction products,* led to an amine fraction consisting very largely (92%) of the product **2** of syn $S_N2'$ displacement in addition to ~2% of **4**.

We have extended this finding to the cis isomer **3**, R = 2,4,6-trimethylbenzoyl, and find that under the above conditions (28% completion), the major product is that of syn $S_N2'$ displacement, **4** (80%), accompanied by 20% of the (inverted) $S_N2$ product. The product of anti $S_N2'$ displacement was not found. This last result rules out a common intermediate in the reactions of the esters corresponding to **1** and **3** and also shows that product stability is not a factor in determining the product stereochemistry.

Reaction of **1**, R = 2,4,6-trimethylbenzoyl (1 M in refluxing butanol), with the sodium salt of propanethiol (2 equiv, 4 h) gave complete reaction.[15] The sulfides formed resulted largely from $S_N2$ displacement (**14**, 68.5%). The $S_N2'$ products were formed in a ~9:1 ratio in favor of syn displacement (28% **5**, 3.5% **6**). The ratio in favor of syn $S_N2'$ displacement was decreased in hexamethylphosphoramide (0.1 M in **1**, R = 2,4,6-trimethylbenzoyl, 70 °C, 21 h, 9 equiv of PrSNa) to ~60:40 (28% **5**, 12% **6** in addition to 60% $S_N2$ product **14**).[16] Finally, in opposition to the exclusive syn $S_N2'$ result with piperidine and **3**, R = 2,4,6-trimethylbenzoyl, the latter compound now gave, under the propylthiolate in butanol conditions, a syn to anti ratio of 35:65 (17.5% **5**, 32.5% **6**; in addition to 50% $S_N2$ product, **13**). All these ratios are completely different from those obtained under solvolysis conditions (refluxing with propanethiol for 18 h) which, in contrast to the bimolecular displacement above, gave both **13** and **14** from the mesitoates corresponding to either **1** or **3**.[17]

It is clear that there appears to be a spectrum of $S_N2'$ reactions in cyclohexenyl systems. Because of the very real possibility of a bias particular to the six-membered system, it is highly desirable to consider the situation in acyclic cases. The next communication deals with this problem.

**Acknowledgment.** We thank the National Science Foundation for its support of this work.

## References and Notes

(1) G. Stork and W. N. White, *J. Am. Chem. Soc.*, **75**, 4119 (1953); **78**, 4609 (1956).
(2) The reaction gave a mixture consisting, in order of decreasing retention times on 5% FFAP: **1**, R = H (59%); **3**, R = H (20%); *trans*-2-isopropylcyclohexanol (13%); *cis*-2-isopropylcyclohexanol (6%); 2-isopropylcyclohexanone (2%).
(3) Purified by silica gel chromatography using 95:5 pentane–ether. All identifications were by NMR, IR, VPC, and GC–MS (the latter on a Finnigan Model 3300 spectrometer).
(4) G. Vavon and A. Callier, *Bull. Soc. Chim. Fr.*, **41**, 357 (1927).
(5) H. C. Brown and S. Krishnamurthy, *J. Am. Chem. Soc.*, **94**, 7159 (1972).
(6) Unlike the 2,6-dichlorobenzoates, the mesitoates derived from **1,3**, **13,14**, R = H, were stable to VPC. They had retention times of 11.4, 10.31, 15.0, and 22.1 min, respectively, on 1.5% OV-101 at 190 °C. They, and the dichlorobenzoates, could be reconverted to the pure parent alcohol by reduction with diisobutylaluminum hydride. Lithium aluminum hydride was not suitable, giving partially isomerized products.
(7) P. Anziani and R. Cornubert, *Bull. Soc. Chim. Fr.*, 857 (1948).
(8) The four isomeric saturated amines **7**, **8**, **9**, and **10** were cleanly separated by gas phase chromatography and showed retention times of 6.19, 5.81, 7.19, and 8.06 min, respectively, on 5% SE 30 at 190 °C.
(9) M. M. Green and B. B. Roy, *J. Am. Chem. Soc.*, **92**, 6368 (1970).
(10) P. Bickart, F. W. Carson, J. Jacobus, E. G. Miller, and K. Mislow, *J. Am. Chem. Soc.*, **90**, 4869 (1968). The intermediate sulfenates were made by reaction of the lithium salts of the alcohols with *S*-propyl *p*-toluenethiosulfonate made with propyl iodide in dimethylformamide; cf. J. P. Weidner and S. S. Block, *J. Med. Chem.*, **7**, 671 (1964).
(11) The allylic sulfides, **5**, **6**, **13**, and **14**, were obtained as colorless liquids after silica gel chromatography (pentane elution). Their respective retention times (5% FFAP) were **13** < **14** < **6** < **5**.
(12) A. K. Macbeth and J. S. Shannon, *J. Chem. Soc.*, 2852 (1952).
(13) The cis alcohol was also the more rapidly eluted isomer on vapor phase chromatography (5% FFAP, 175 °C).
(14) The rearranged dichlorobenzoates were those corresponding to **12** and **3** (16 and 4%) as determined by gas chromatography of the allylic alcohols from Dibal reduction of the recovered esters.
(15) Starting mesitoates and product sulfides were shown to be stable under the reaction conditions. Identification of products was by gas chromatography–mass spectrometry (cf. footnotes 6 and 11).
(16) There was only 5% of attack at carbonyl (with formation of **1**, R = H) in this case, in contrast to 39% from the reaction in butanol.
(17) The four sulfides **5**, **6**, **13**, and **14** were obtained in the relative percentages 22, 38, 10, and 30% and 14, 54, 15, and 17% from **1** and **3**, R = mesitoyl, respectively.

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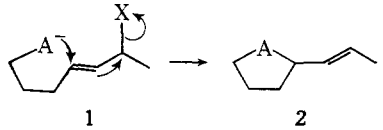
## Concerning the Stereochemistry of the $S_N2'$ Reaction. "Concerted" Allylic Displacement in an Acyclic System: Anti Displacement with Thiolate Anion

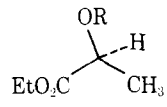
*Sir:*

"Concerted" displacement with rearrangement in allylic cyclohexenyl systems ($S_N2'$) takes place largely with syn relationship of the entering and departing groups, when the displacing group is piperidine. With thiolate anion, however, considerable product from anti displacement is obtained.[1] This communication reports our findings that the internal counterpart of the $S_N2'$ reaction ($S_N'$) with thiolate anion (**1**, A = S, → **2**) takes place anti to the departing group in an acyclic system. The choice of an internal displacement was made to avoid complications relating to partition of products between $S_N2$ and $S_N2'$ types and also because of the existence of a previous, apparently well-authenticated case,[2] of this type in

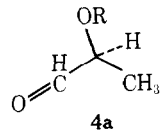


which the product in a transformation of the type **1** → **2**, in which A- was a carbanion, had a structure best rationalized as a displacement syn to the departing substituent.

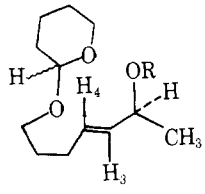
The starting material for this study was made from (*S*)-(−)-ethyl lactate $[\alpha]_D$ −11.1° (neat) via the benzyloxymethyl ether **3a**,[3] $[\alpha]^{25}_D$ −48.3° (*c* 1.73, 95% ethanol) (benzyl chloromethyl ether, *N,N*-diisopropylethylamine, room temperature overnight), and the aldehyde **4a**, $[\alpha]^{25}_D$ −26.5° (*c* 1.464, THF) (lithium aluminum hydride–ether, Collins oxidation;[4] 48% from **3a**). Reaction of **4a** with the phosphorane derived from the tetrahydropyranyl ether of 4-bromobutanol, essentially under Schlosser conditions,[5] gave the trans olefin **5a**, $[\alpha]^{25}_D$ −84.3° (*c* 1.63, 95% ethanol), 69% after purification. NMR: δ 5.32 ($H_3$, dd, *J* = 16, 6 Hz), 5.70 ($H_4$, dt, *J* = 16, 6 Hz). Removal of the benzyloxymethyl group (lithium–ammonia–THF–aniline) gave **5**, $[\alpha]^{25}_D$ −10.0° (*c* 1.65, ether), as a colorless liquid (silica gel, 6:4 pentane–ether). The optical purity, measured by Mosher's method[7] ($^{19}$F NMR) was ~76%. Transformation of **5** into **6** was accomplished by treatment of the lithium salt of **5** (methyl lithium–ether, −30 °C) with mesitoyl chloride, followed by removal of the tetrahydropyranyl protecting group (4:1 acetone–0.1 N sulfuric acid, 30 min reflux). The hydroxy mesitoate **6**, $[\alpha]^{25}_D$ +19.4° (*c* 2.80, ether), was finally transformed to the required (*S*)-(+)-mesitoate of 7-acetylmercapto-3-hepten-2-ol (**7**), $[\alpha]^{25}_D$ +12.7° (*c* 0.47, ether). NMR δ 1.40, 3 H, d, *J* = 6 Hz; 1.65, 2 H, m; 2.13, 2 H, m; 2.26, 9 H, s; 2.30, 3 H, s; 2.87, 2 H, t, *J* = 7 Hz; 5.66, 3 H, m; 6.82, 2 H, s.



**3**, R = H
**3a**, R = $PhCH_2OCH_2$



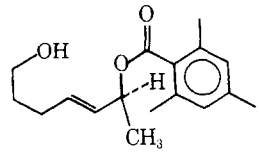
**4a**



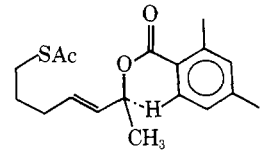
**5**,**5a**

Cyclization of the thiol anion formed in situ from its acetate **7** under a variety of basic conditions took place readily to produce a mixture of *Z* and *E* isomers of 2-propenyl tetrahydrothiophene (**8**). Because a given concerted displacement (syn or anti) must lead to opposite absolute configurations in the *Z* and *E* isomers of **8**, we were gratified to find that cyclization of **7** with lithium methoxide (10 equiv in THF, 30 h, room temperature, in the dark under argon) gave, after purification, 52% yield of **8** which was shown by NMR, TLC, IR, and VPC analysis to consist of an *E*:*Z* ratio of 93:7.[8] The rotation of **8** thus obtained was $[\alpha]^{25}_D$ +134° (*c* 0.66, THF).

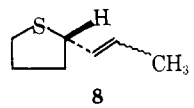
Authentic (*S*)-(+)-(*E*)-2-propenyltetrahydrothiophene (**8**) was synthesized starting with (*S*)-(+)-tetrahydrothiophene-2-carboxylic acid (**9**), $[\alpha]_D$ +98° (*c* 2.48, 95% ethanol),[9] by first making the corresponding aldehyde **10**, $[\alpha]^{25}_D$ +78.2° (*c* 1.41, 95% ethanol) (reduction of the methyl ester (ex diazomethane), with diisobutylaluminum hydride, −78 °C) followed by Schlosser–Wittig reaction[4] with ethyl triphenylphosphonium bromide. The authentic *E* isomer of **8** (*E*:*Z* = 97:3), $[\alpha]^{25}_D$ +79.2° (*c* 0.582, THF), thus obtained was easily differentiated from the *Z* isomer obtained from the usual Wittig reaction (*Z*:*E* = 94:6), $[\alpha]^{25}_D$ +94.3° (*c* 0.802, THF), by its shorter retention time on 20% TCEP at 108 °C.



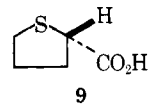
**6**



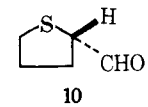
**7**



**8**



**9**



**10**

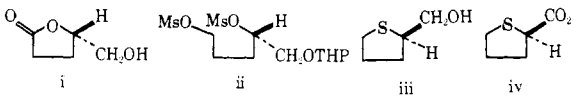
Since the optical purity of **10** was ~39%, the rotation of the pure (*S*)(+) *E* isomer **8** should be ~+200° and since the optical purity of our (*S*)-(+)-**7** was at most 76% (vide supra), it follows that the $S_N2'$ cyclization of (*S*)-(+)-**7** to (*S*)-(+)-**8** has taken place very largely, and possibly entirely, *by addition of the thiolate ion anti to the departing mesitoate:* what appeared as a trend, with thiolate ion, in the cyclohexenyl series is apparently the major pathway in acyclic systems.

The present results, especially when taken together with those of ref 2, suggest that the stereochemistry of the intramolecular process may be greatly affected, inter alia, by the nature of the displacing and departing groups. Further work would seem warranted on this matter since the intramolecular version of the $S_N2'$ reaction would seem to have considerable synthetic potential. Until such further data become available, it is of passing interest that practically all theoretical treatments of the $S_N2'$ reaction have concluded that there should be a syn relation of entering and departing groups.[10,11]

**Acknowledgment.** We wish to thank the National Science Foundation for its support of this work.

## References and Notes


(1) G. Stork and A. F. Kreft III, *J. Am. Chem. Soc.*, preceding paper in this issue.
(2) J. Martel, E. Toromanoff, J. Mathieu, and G. Nominé, *Tetrahedron Lett.*, 1491 (1972).
(3) All the substances mentioned were purified by chromatography on neutral silica gel (elution with pentane–ether) and gave NMR, IR, and mass spectra in agreement with their postulated structures. Optical rotations were taken on a Perkin-Elmer Model 141 polarimeter.
(4) J. C. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Lett.*, 3363 (1968).
(5) M. Schlosser and K. F. Christman, *Angew. Chem., Int. Ed. Engl.*, **5**, 126 (1966). *tert*-Butyl alcohol was used instead of anhydrous hydrogen chloride as a proton source.
(6) J. A. Dale and H. S. Mosher, *J. Am. Chem. Soc.*, **95**, 512 (1973).
(7) High pressure liquid chromatography (98:2 hexane–isoproyl alcohol, Porasil A) and comparison with the cis compound derived from the standard Wittig reaction on **4a** showed the substance to be ~98% (*E*). The two diastereoisomers (tetrahydropyran asymmetry) of (*Z*) **5** were eluted before the (unresolved) (*E*) and had their vinyl hydrogens at δ 5.48 (m). The structure of **5** was further confirmed by its identity (NMR, IR, TLC) with the isomer, independently synthesized by lithium aluminum hydride reduction (in THP–sodium methoxide) of the acetylenic analogue of **5**.
(8) The *Z*/*E* ratio in the product **8** showed a remarkable dependence on both the solvent (lithium salt in hexamethylphosphoramide, *Z*/*E* = 32/68), or the counterion (sodium salt in THF, *Z*/*E* = 26/74). The larger amount of the less stable *Z* isomer with looser ion pairs may reflect an earlier transition state.
(9) G. Claeson and H. G. Jonsson, *Arkiv. Kemi*, **26**, 247 (1966). The optical purity was determined to be ~39% by Mosher's method on the alcohol (G. Claeson and H. G. Jonsson, *ibid.*, **31**, 83 (1969)) from **10** and lithium aluminum hydride. The assignment of the configuration shown in formula **9** to the (+)-tetrahydrothiophene-2-carboxylic acid is crucial to the validity of the results of this paper. The literature assignment lacks rigor because of mechanistic uncertainties in the reactions which were used (G. Claeson and H G. Jonsson, loc. cit.), and we have, therefore, rigorously established that the previous assignment of the chirality shown in **9** to the (+) acid is correct. (*S*)-(+)-4,5-Dihydroxypentanoic acid 1,4-lactone (i), of unambiguous chirality (K. Koga, M. Taniguchi, and S. Yamada, *Tetrahedron Lett.*, 263 (1971)), was reduced (lithium aluminum hydride) as its tetrahydropyranyl ether to the diol which, via the dimesylate (ii), and reaction with sodium sulfide (methanol, room temperature, overnight), followed by dilute acid hydrolysis, gave (−)-2-tetrahydrothiophenemethanol (iii) $[\alpha]^{25}_D$ −81.5° (*c* 2.06 in chloroform). Since the same alcohol ($[\alpha]^{23}_D$ −84°) has been obtained by lithium aluminum hydride reduction of (−)-tetrahydrothiophene-2-carboxylic acid (G. Claeson and H.G. Jonsson, *Ark. Kemi*, **31**, 83 (1969)), the latter is indeed correctly represented by iv, and the (+) antipode used in this work has the chirality shown in **9**.



i ii iii iv

We are greatly indebted to Dr. Yuko Nakahara of this Laboratory for this unambiguous synthesis.

(10) K. Fukui and H. Fujimoto, *Bull. Chem. Soc. Jpn.*, **40**, 2018 (1967); W. Drenth, *Recl. Trav. Chim. Pays-Bas*, **86**, 318 (1967); N. T. Anh, *Chem. Commun.*, 1089 (1968); W. Jefford and U. Burger, *Chimia*, **25**, 297 (1971); C. L. Liotta, *Tetrahedron Lett.*, 523 (1975). A recent suggestion has been made that the $S_N2'$ should be syn with neutral, but anti with anionic, displacing groups (R. L. Yates, N. D. Epiotis, and F. Bernardi, *J. Am. Chem. Soc.*, **97**, 6615 (1975). This is an interesting, but certainly insufficient,[1] suggestion.

(11) There has been considerable discussion whether concerted $S_N2'$ reactions ever occur (F. G. Bordwell, *Acc. Chem. Res.*, **3**, 281 (1970)). They have been said to be "intellectually unreasonable" or "abhorrent" (R. A. Sneen and J. V. Carter, *J. Am. Chem. Soc.*, **94**, 6990 (1972), and footnote 26). These arguments are really concerned with the extent of bond breaking and bond forming at the transition state. It would not be surprising to find that these parameters vary from case to case. See also, in another context, W. H. Saunders, Jr., *Acc. Chem. Res.*, **9**, 9 (1976), and D. J. McLennan, *ibid.*, **9**, 281 (1976).

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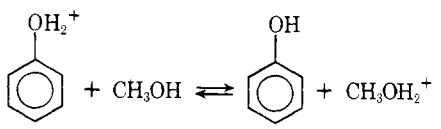
## The Proton Affinities of Phenol

*Sir:*

Phenol and various of its derivatives are known in solution to protonate both at oxygen and on the aromatic ring.[1] The relative extent of protonation at the two sites depends not only on the detailed pattern of substitution, but also on temperature and on the nature of the solvent system. For example, the ratio of oxygen to ring protonation in *p*-cresol varies from 5.5 in pure fluorosulfonic acid to nearly zero in a solution which is 30% by weight $SbF_5$.[1c] The complex behavior of such systems in solution has seriously hampered attempts at unraveling the electronic structure of either the oxygen or ring protonated ions and has made it difficult to establish the degree to which a phenyl ring influences protonation at oxygen or a hydroxy or alkoxy group affects reaction on the aromatic ring.

In this communication, we describe the results of our combined experimental and theoretical efforts to obtain a quantitative measure of the relative affinities for oxygen and ring protonation of phenol in the gas phase. Our data should enable assessment of both the magnitudes of specific interactions between the phenyl and hydroxy groups and of the influence of solvent on the site of protonation.

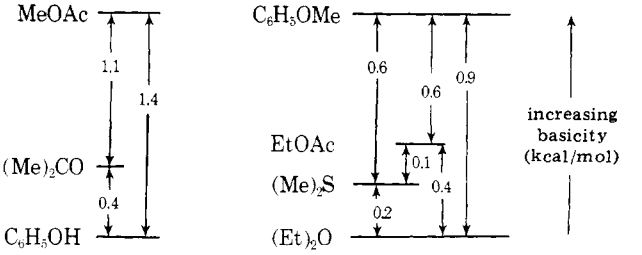
Both the oxygen and ring proton affinities of phenol may be estimated using quantitative molecular orbital calculations. The oxygen proton affinity of phenol may be estimated by biasing the experimental proton affinity of methanol (182.2 kcal/mol[2]) by the calculated energy for the *isodesmic*[3] process,



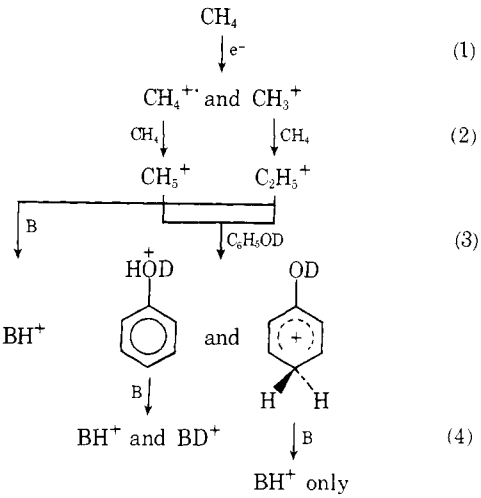
$\Delta E$(STO-3G)[4,5] = −1.0 kcal/mol

relating the two basicities. The value arrived at in this manner (181.2 kcal/mol) is far smaller than the experimental proton affinity of phenol (195.5 kcal/mol), as determined by pulsed ion cyclotron resonance equilibrium experiments[8] using the method of multiple overlaps[2a] (Scheme I). Such a value is in good accord with a recent determination of the proton affinity of phenol of 195.0 kcal/mol using high pressure mass spectrometry.[9] The theory's estimate for the energy of protonation of phenol on the aromatic ring is obtained by biasing $\Delta E$ for

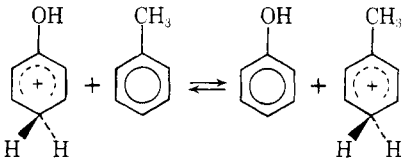
Scheme I




Scheme II




the reaction shown below by the experimental proton affinity of toluene (188.7 kcal/mol).[2a,10] This value of 196.1 kcal/mol



$\Delta E$(STO-3G) = 7.4 kcal/mol

is in reasonable agreement with the measured proton affinity of phenol. It appears, therefore, that, in the absence of solvent, phenol protonates on the aromatic ring,[11] and that the energetic preference over oxygen protonation is sizable (~15 kcal/mol).

We have devised a labeling experiment to provide us with a semiquantitative estimate of the enthalpy for protonation of phenol at oxygen. The predominant ion–molecule reactions which take place when a mixture of methane, $C_6H_5OD$, and a base B of known proton affinity is added to a pulsed ICR spectrometer (in proportions of 100:10:1, respectively) are shown in Scheme II. Electron impact produces $CH_4^+$ and $CH_3^+$ predominantly which react rapidly with the methane buffer gas to generate $CH_5^+$ and $C_2H_5^+$. Both of these ions react exothermically with phenol to produce both the ring and the oxygen protonated forms and with B to produce $BH^+$. If the proton affinity of the base B is sufficiently high, it is able to deprotonate phenol. The main feature of this experiment for estimating the enthalpy for protonation of phenol at oxygen is that an ion of *m/e* corresponding to $BD^+$ will be observed only if reaction of B with the oxygen protonated phenol is exothermic, thermoneutral, or slightly ($\leq$1 or 2 kcal/mol) endothermic. Bases with proton affinities significantly lower than phenol protonated at oxygen will not extract deuterium, while bases with equal or greater proton affinities will show $BD^+$ in their mass spectra. By using a series of bases of increasing strength and by monitoring the onset of production of $BD^+$, it should, therefore, be possible to determine an ap-