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Solvent Effect on the Optical Rotation of (*S*)-(–)-α-Methylbenzylamine

G. G. Midyana[a], R. G. Makitra†[a], and E. Ya. Pal'chikova[b]

[a] *Department of Physical Chemistry of Fossil Fuels InPOCC, National Academy of Sciences of Ukraine,*
ul. Naukova 3a, Lviv, 79053 Ukraine
e-mail: gmidyana@gmail.com

[b] *Institute of Geology and Geochemistry of Fossil Fuels, National Academy of Sciences of Ukraine, Lviv, Ukraine*

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Abstract—The relation between the optical rotation of (*S*)-(–)-α-methylbenzylamine and solvent properties can be described by multiparameter equations. The determining factors in relatively neutral solvents are specific and nonspecific solvation. The $[\alpha]_D$ value in polar solvents depends only on specific solvation, whereas the polarizability factor is insignificant. Steric hindrances and self-association are insignificant in neutral media, and an appreciable reduction of the $[\alpha]_D$ value is likely to result from hindrances to the formation of H-complexes.

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The angle of rotation of linearly polarized light ($[\alpha]_D$) by solutions of optically active compounds is determined by both concentration of the solute and properties of the solvent which affect the dipole moment of the solute due to solvation. However, little success has been achieved in describing variation of $[\alpha]_D$ in terms of a single factor, i.e., using a single solvent parameter. This applies to such characteristics of liquids as refractive index *n*, dielectric permittivity ε [1], molar volume [2], polarization, and others. No unambiguous results were obtained by quantum mechanical analysis of solvent effects on $[\alpha]_D$ [3]. This is not surprising, taking into account that interaction between a solvent and a solute is a complex process determined by a number of different factors [4, 5]. Therefore, solvent effect on the dissolved substance, including change of configuration of the latter and hence its dipole moment responsible for the $[\alpha]_D$ value, is the result of joint action of all factors. Relation between the solute and solvent properties may be derived on the basis of the linear free energy relationship principle by considering overall effect of particular energy constituents originating from different types of solvation [4–6].

Menucci et al. [7] studied variation of optical activity of terpenes in various solvents and found that $[\alpha]_D$ values change in a complicated manner depending on both terpene structure (including the presence or absence of a carbonyl group in terpene molecule) and solvent nature. Depending on the solvent, either electrostatic or nonelectrostatic effects may be crucial, but the overall effect is inconsistent with the above theories. However, we have recently shown [8] that the data of [7] can be satisfactorily described in terms of a six-equation based on the linear free energy relationship.

$$[\alpha]_D = a_0 + a_1 f(n^2) + a_2 f(\varepsilon) + a_3 B + a_4 E_T + a_5 \delta^2 + a_6 V_m. \quad (1)$$

This equation comprises both nonspecific solvation, which is determined by polarizability $f(n^2)$ and polarity $f(\varepsilon)$ of the solvent, and possible specific solvation which depends on the solvent basicity B and electrophilicity E_T, as well as self-association of solvent molecules (given by the squared Hildebrand solubility parameter δ^2) and molar volume V_m. The significance of each term of Eq. (1) with respect to $[\alpha]_D$ and even the sign of the corresponding coefficient are related to structural features of particular terpene, specifically to the presence and position in its molecule of a carbonyl group which is subject to electrophilic solvation. It should be noted that in almost all cases the deter-

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† Deceased.

mining factor is nonspecific solvation of terpene molecule, especially the one originating from solvent polarizability.

On the other hand, the use of Eq. (1) to generalize the data of [9] on $[\alpha]_D$ of propylene oxide possessing a readily accessible oxygen atom revealed that specific solvation is significant: solvent polarizability and basicity increased $[\alpha]_D$ value, whereas electrophilic solvation reduced it [10].

Taking the above data into account, it seemed reasonable to analyze solvent effects on the optical activity of compounds whose asymmetric moiety contains a nitrogen atom which is a stronger electron donor than oxygen. Fischer et al. [11, 12] studied the optical activity of (*S*)-(–)-α-methylbenzylamine in 39 solvents (Tables 1, 2). Among these, all parameters required for calculation by Eq. (1) are known for 36 solvents [13, 14]. However, the correlation obtained for 36 solvents was characterized by unsatisfactorily low multiple correlation coefficient (R = 0.713), and only exclusion of deviating data for 12 solvents (i.e., 1/3) gave Eq. (2) with an acceptable value of R (≥ 0.95).

$$\begin{aligned}[\alpha]_D = &-110.8084 + (88.3312\pm12.2311)f(n^2)\\ &- (36.3312\pm7.8263)f(\varepsilon) - (0.0003\pm0.0036)B\\ &+ (1.2881\pm0.1559)E_T + (0.0082\pm0.0066)\delta^2\\ &+ (0.0487\pm0.0139)V_m; \qquad (2)\\ &R = 0.9582,\ s = \pm1.6849.\end{aligned}$$

Successive exclusion of insignificant terms led to four-parameter Eq. (3) which describes the relation between $[\alpha]_D$ and solvent properties with a sufficient accuracy.

$$\begin{aligned}[\alpha]_D = &-103.8475 + (95.2184\pm11.2212)f(n^2)\\ &- (34.9439\pm7.1336)f(\varepsilon) + (1.4137\pm0.1237)E_T\\ &+ (0.0411\pm0.0117)V_m; \qquad (3)\\ &R = 0.9563,\ s = \pm1.7421.\end{aligned}$$

The effect of solvent molar volume on $[\alpha]_D$ is also relatively insignificant; removal of the corresponding term from Eq. (3) reduces the R value to 0.9322. Thus, the main factors influencing the optical activity of α-methylbenzylamine are nonspecific solvation determined by the solvent polarizability and electrophilic solvation. These factors affect steric configuration of solute molecules and their dipole moment, and elimination of either factor from Eq. (3) destroys the correlation.

Table 1 contains both experimental $[\alpha]_D$ values and those calculated by Eq. (3), as well as the differences between these values ($\Delta[\alpha]_D$). Figure 1 shows the correlation $[\alpha]_{D,\ calc}$–$[\alpha]_{D,\ exp}$ for the solvents included in Eq. (3). It is seen that in most cases Δα values are within the error range s ±1.742, and they do not exceed ±s.

Insofar as the excluded solvents (Table 1) were mainly potent hydrogen bond donors (alcohols, $CHCl_3$, etc.), it may be presumed that hydrogen bonds formed by these solvents with the amine molecule essentially affect configuration of the latter, and the resulting complex may be characterized by a different optical activity. In order to explore this problem in more detail, we collected in Table 2 the data for all solvents excluded while deriving Eq. (3) and the data for all alcohols. Taking into account that hydrogen bonding is governed by electrophilic solvation, Fig. 2 shows the

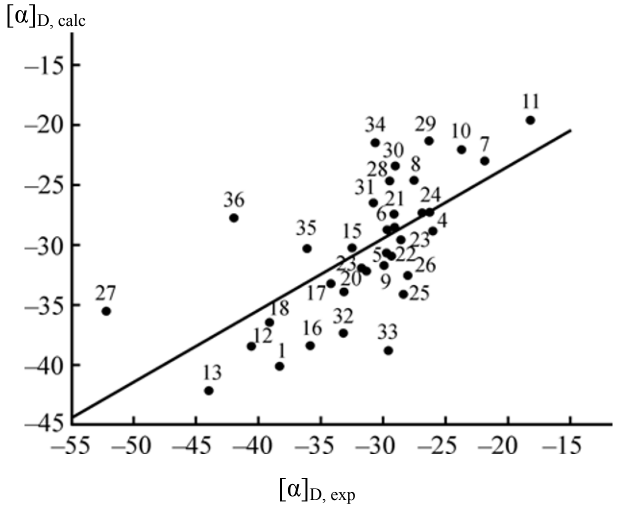

Fig. 1. Correlation between the experimental $[\alpha]_D$ values of (*S*)-(–)-α-methylbenzylamine and those calculated by Eq. (3). For solvent numbering, see Table 1.

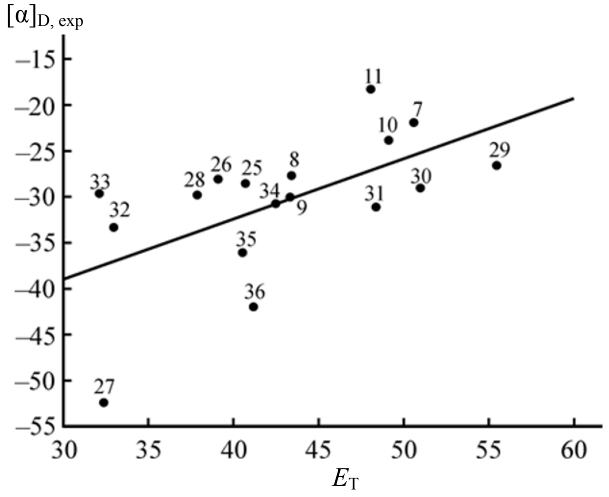

Fig. 2. Correlation between the experimental $[\alpha]_D$ values of (*S*)-(–)-α-methylbenzylamine and solvent electrophilicity parameters E_T. For solvent numbering, see Tables 1, 2.

Table 1. Experimental [11] $[\alpha]_D$ values of (*S*)-(–)-α-methylbenzylamine and those calculated by Eq. (3)

Run no.	Solvent	$[\alpha]_{D,\ exp}$	$[\alpha]_{D,\ calc}$	$\Delta[\alpha]_D$
	Values included in Eq. (3)			
1	Pentane	–38.29	–40.13	–1.84
2	Benzene	–31.86	–31.86	0.00
3	Toluene	–31.34	–32.08	–0.74
4	1,2-Dibromoethane	–26.13	–28.91	–2.78
5	Chlorobenzene	–29.66	–30.72	–1.06
6	Bromobenzene	–29.78	–28.75	1.03
7	Propan-1-ol	–21.89	–22.97	–1.08
8	2-Methylpropan-1-ol	–27.58	–24.61	2.97
9	2-Methylpropan-2-ol	–29.96	–31.77	–1.81
10	Pentan-1-ol	–23.75	–22.05	1.70
11	Octan-1-ol	–18.20	–19.60	–1.40
12	Cyclohexane	–40.62	–38.40	2.22
13	Diethyl ether	–44.04	–42.08	1.96
14	Dibenzyl ether	–26.88	–27.28	–0.40
15	Methoxybenzene	–32.45	–30.20	2.25
16	Tetrahydrofuran	–35.89	–38.40	–2.51
17	1,4-Dioxane	–34.17	–33.33	0.84
18	Acetone	–39.10	–36.48	2.62
19	*N*,*N*-Dimethylaniline	–29.11	–28.54	0.57
20	Acetonitrile	–33.18	–33.83	–0.65
21	Benzonitrile	–29.14	–27.38	1.76
22	Nitromethane	–29.34	–30.84	–1.50
23	Hexamethylphosphoramide	–28.60	–29.43	–0.83
24	Dimethyl sulfoxide	–26.25	–27.19	–0.94
	Values excluded from Eq. (2)			
25	Methylene chloride	–28.29	–34.11	–5.82
26	Chloroform	–28.05	–32.53	–4.48
27	Carbon tetrachloride	–52.29	–35.61	16.68
28	Iodobenzene	–29.53	–24.52	5.01
29	Methanol	–26.38	–21.33	5.05
30	Ethanol	–28.99	–23.44	5.55
31	Propan-2-ol	–30.81	–26.51	4.30
32	Dibutyl ether	–33.23	–37.35	–4.12
33	Triethylamine	–29.62	–38.76	–9.14
34	*N*-Methylaniline	–30.65	–21.48	9.17
35	Pyridine	–36.09	–30.23	5.86
36	Nitrobenzene	–41.92	–27.70	14.22

correlation $[\alpha]_{D,\,exp}$–E_T. Interestingly, the $[\alpha]_D$ value of (*S*)-(–)-α-methylbenzylamine in such strong hydrogen bond donors as lower alcohols, chloroform, and methylene chloride remains almost constant (29 ± 1); however, the optical rotations measured in higher alcohols deviate from the above dependence toward lower values, presumably due to steric hindrances to H-bonding created by bulky alkyl substituents. On the other hand, the $[\alpha]_D$ values in pyridine, triethylamine, nitrobenzene, and carbon tetrachloride are higher. This suggests a more complex mechanism of interaction between α-methylbenzylamine with the solvent. Generalization of all (17) $[\alpha]_D$ values in Table 2 by Eq. (1) afforded $R = 0.8883$, and exclusion of the data for methanol, triethylamine, iodobenzene, and dibutyl ether gave Eq. (4):

$$\begin{gathered}[\alpha]_D = -109.8240 - (1.4966 \pm 28.4481) f(n^2) \\ + (27.9768 \pm 14.5745) f(\varepsilon) - (0.0048 \pm 0.0047) B \\ + (3.5525 \pm 0.3848) E_T - (0.1630 \pm 0.0177) \delta^2 \\ - (0.1243 \pm 0.0342) V_m; \qquad (4) \\ R = 0.9769,\ s = \pm 1.8801.\end{gathered}$$

Subsequent exclusion of insignificant terms led us to Eq. (5):

$$\begin{gathered}[\alpha]_D = -107.0745 + (3.6635 \pm 0.3408) E_T \\ - (0.1562 \pm 0.0202) \delta^2 - (0.1294 \pm 0.0357) V_m; \qquad (5) \\ R\ 0.9670,\ s \pm 2.2422.\end{gathered}$$

It should be noted that correlation (5) does not include the specific optical rotation for donor morpholine ($[\alpha]_D$ = 28.49), which was also not included in the calculation by Eq. (4) because of the lack of the corresponding paremater *B*. The $[\alpha]_D$ value calculated by Eq. (5) (43.29) considerably exceeds the experimental value.

Here, it is worth noting that the optical activity of α-methylbenzylamine in relatively neutral organic solvents [Eqs. (2), (3)] is determined by both specific and nonspecific solvation. If a fairly strong hydrogen bond is formed between the amine and solvent [Eqs. (4), (5)], the $[\alpha]_D$ values correlate only with specific electrophilic solvation, whereas the polarizability factor (nonspecific solvation) is insignificant. On the other hand, steric hindrances (V_m) and self-association are insignificant for neutral media where appreciable reduction of $[\alpha]_D$ values is likely to be determined by hindrances to formation of H-complexes.

Table 2. Experimental $[\alpha]_D$ values of (*S*)-(–)-α-methylbenzylamine in alcohols and solvents excluded from Eq. (2) and $[\alpha]_D$ values calculated by Eq. (5)

Run no.	Solvent	$[\alpha]_{D,\,exp}$	$[\alpha]_{D,\,calc}$	$\Delta[\alpha]_D$	E_T
7	Propan-1-ol	–21.89	–23.24	–1.35	50.7
8	2-Methylpropan-1-ol	–27.58	–23.83	3.75	43.4
9	2-Methylpropan-2-ol	–29.96	–32.72	–2.76	43.3
10	Pentan-1-ol	–23.75	–22.31	1.44	49.1
11	Octan-1-ol	–18.20	–19.87	–1.67	48.1
25	Methylene chloride	–28.29	–30.36	–2.07	40.7
26	Chloroform	–28.05	–29.39	–1.34	39.1
27	Carbon tetrachloride	–52.29	–49.46	2.83	32.4
28	Iodobenzene[a]	–29.53	–43.79	–14.26	37.9
29	Methanol[a]	–26.38	–46.19	–19.81	55.4
30	Ethanol	–28.99	–30.07	–1.08	51.0
31	Propan-2-ol	–30.81	–27.67	3.14	48.4
32	Dibutyl ether[a]	–33.23	–43.20	–9.97	33.0
33	Triethylamine[a]	–29.62	–40.78	–11.16	32.1
34	*N*-Methylaniline	–30.65	–29.47	1.18	42.5
35	Pyridine	–36.09	–35.83	0.26	40.5
36	Nitrobenzene	–41.92	–44.23	–2.31	41.2

[a] Excluded solvents.

It should be emphasized that our results are more satisfactory than the data reported in [11] where the authors made an attempt to correlate specific optical rotation of α-methylbenzylamine with different solvent parameters, as well as to perform multiple variable analysis with the use of Kamlet–Taft–Abraham parameters [15].

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